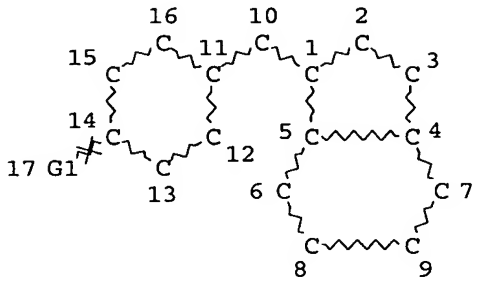
=> d que stat l7
L5 STR



S @18 Se @19

VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

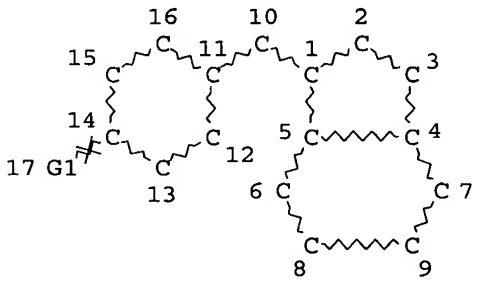
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
L7 856 SEA FILE=REGISTRY SSS FUL L5

100.0% PROCESSED 58369 ITERATIONS 856 ANSWERS
SEARCH TIME: 00.00.01

=> d que stat l12'
'L12'' IS NOT VALID HERE
For an explanation, enter "HELP DISPLAY QUERY".

=> d que stat l12
L5 STR



S @18 Se @19

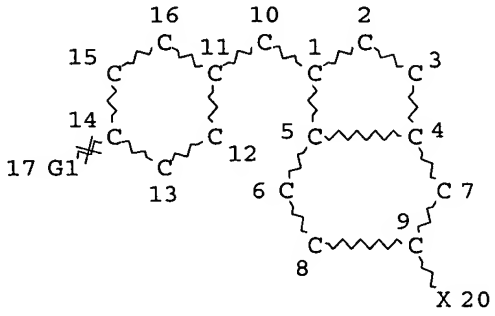
VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
L7 856 SEA FILE=REGISTRY SSS FUL L5
L10 STR

S @18 Se @19



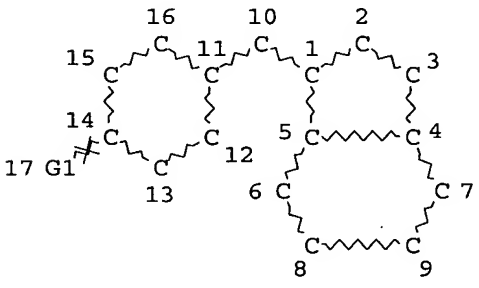
VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L12 622 SEA FILE=REGISTRY SUB=L7 SSS FUL L10

100.0% PROCESSED 643 ITERATIONS 622 ANSWERS
SEARCH TIME: 00.00.01

=> d que stat l18
L5 STR



S @18 Se @19

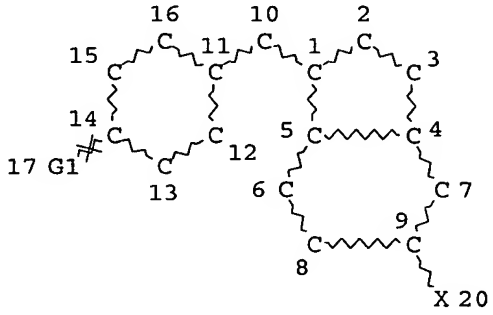
VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
L7 856 SEA FILE=REGISTRY SSS FUL L5
L10 STR

S @18 Se @19

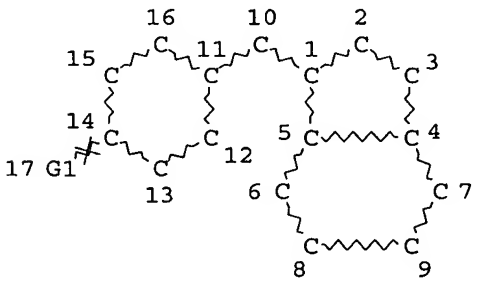


VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L12 622 SEA FILE=REGISTRY SUB=L7 SSS FUL L10
L15 50 SEA FILE=REGISTRY ABB=ON PLU=ON L12 AND S>1
L16 0 SEA FILE=REGISTRY ABB=ON PLU=ON L12 AND SE>1
L17 0 SEA FILE=REGISTRY ABB=ON PLU=ON L12 AND S/ELS AND SE/ELS
L18 50 SEA FILE=REGISTRY ABB=ON PLU=ON (L15 OR L16 OR L17)

=> d que stat l20
L5 STR



S @18 Se @19

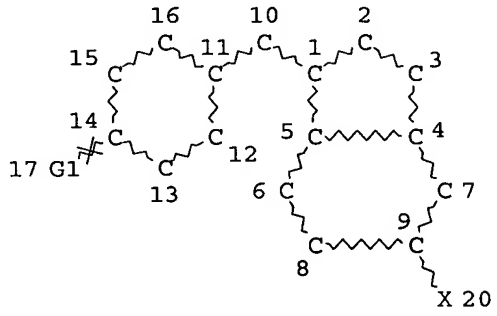
VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
L7 856 SEA FILE=REGISTRY SSS FUL L5
L10 STR

S @18 Se @19

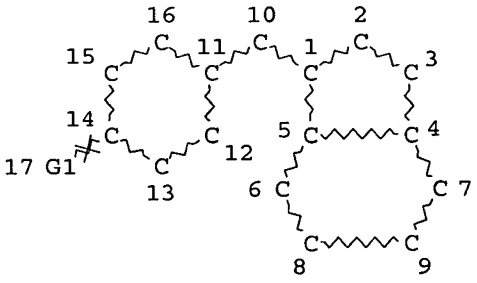


VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L12 622 SEA FILE=REGISTRY SUB=L7 SSS FUL L10
L15 50 SEA FILE=REGISTRY ABB=ON PLU=ON L12 AND S>1
L16 0 SEA FILE=REGISTRY ABB=ON PLU=ON L12 AND SE>1
L17 0 SEA FILE=REGISTRY ABB=ON PLU=ON L12 AND S/ELS AND SE/ELS
L18 50 SEA FILE=REGISTRY ABB=ON PLU=ON (L15 OR L16 OR L17)
L20 29 SEA FILE=REGISTRY ABB=ON PLU=ON L18 AND N/ELS

=> d que stat l24
L5 STR



S @18 Se @19

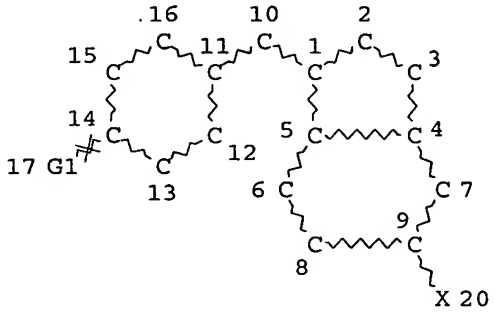
VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

```
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  19

STEREO ATTRIBUTES: NONE
L7          856 SEA FILE=REGISTRY SSS FUL L5
L10             STR
```

S @18 Se @19




```
VAR G1=18/19
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  20

STEREO ATTRIBUTES: NONE
L12         622 SEA FILE=REGISTRY SUB=L7 SSS FUL L10
L15          50 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND S>1
L16           0 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND SE>1
L17           0 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND S/ELS AND SE/ELS
L18          50 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L15 OR L16 OR L17)
L20          29 SEA FILE=REGISTRY ABB=ON  PLU=ON  L18 AND N/ELS
L24             ANALYZE  PLU=ON  L20 1- LC :       8 TERMS


=> d l24 1-8
L24         ANALYZE L20 1- LC :       8 TERMS

TERM #   # OCC  # DOC  % DOC LC
------ ------- ------ ------ ---------------
     1      28     28  96.55 CA
     2      28     28  96.55 CAPLUS
     3      20     20  68.97 TOXCENTER
     4      16     16  55.17 USPATFULL
     5       3      3  10.34 USPAT2
     6       1      1   3.45 IFICDB
     7       1      1   3.45 IFIPAT
     8       1      1   3.45 IFIUDB
*********  END OF L24***

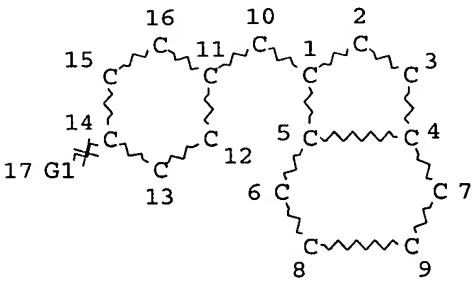

=> d his l28

     (FILE 'HCAPLUS, USPATFULL, USPAT2, TOXCENTER, IFICDB, IFIPAT, IFIUDB'
     ENTERED AT 16:20:33 ON 24 MAR 2006)
```

L28 46 S L26 OR L27
SAVE TEMP L28 VAL809MULS1/A

FILE 'STNGUIDE' ENTERED AT 16:22:35 ON 24 MAR 2006

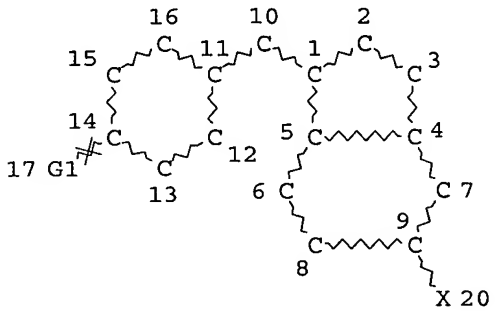
=> d que stat l28
L5 STR



VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
L7 856 SEA FILE=REGISTRY SSS FUL L5
L10 STR



VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

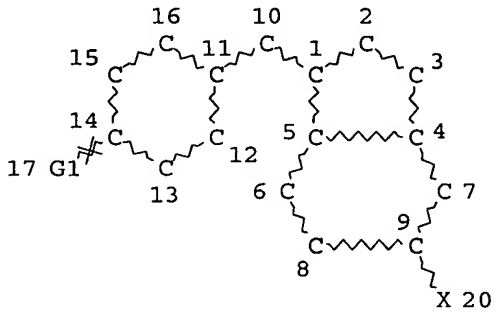
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L12 622 SEA FILE=REGISTRY SUB=L7 SSS FUL L10
L15 50 SEA FILE=REGISTRY ABB=ON PLU=ON L12 AND S>1

```
L16            0 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND SE>1
L17            0 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND S/ELS AND SE/ELS
L18           50 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L15 OR L16 OR L17)
L20           29 SEA FILE=REGISTRY ABB=ON  PLU=ON  L18 AND N/ELS
L25           69 SEA L20
L26           46 DUP REM L25 (23 DUPLICATES REMOVED)
L27           45 SEA L26 AND (AY<2004 OR PY<2004 OR PRY<2004 OR MY<2004 OR
                 REVIEW/DT)
L28           46 SEA L26 OR L27


=> => d que stat l30
L29             STR

S @18    Se @19                                          N 21
```




```
S 23

VAR G1=18/19
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
NSPEC   IS RC     AT  21
NSPEC   IS RC     AT  23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

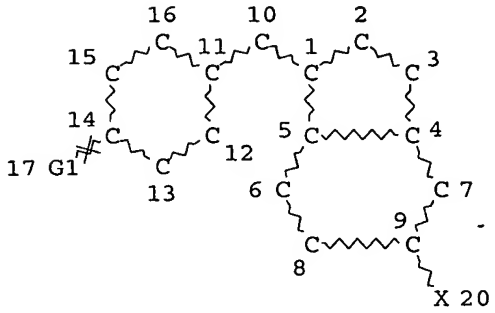
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
L30             0 SEA FILE=BEILSTEIN SSS FUL L29

100.0% PROCESSED     364 ITERATIONS                     0 ANSWERS
SEARCH TIME: 00.00.04


=> d que stat l32
L31             STR
```

S @18 Se @19



N 21

Se 23

VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 21
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

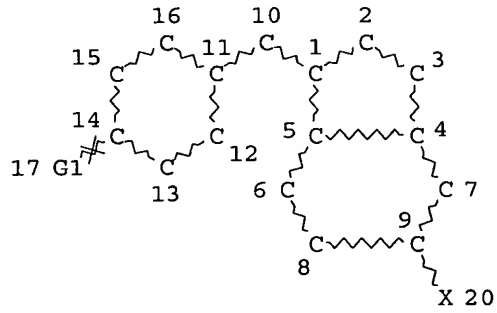
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
L32 0 SEA FILE=BEILSTEIN SSS FUL L31

100.0% PROCESSED 252 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.02

=> d que stat l33
L29 STR

S @18 Se @19



N 21

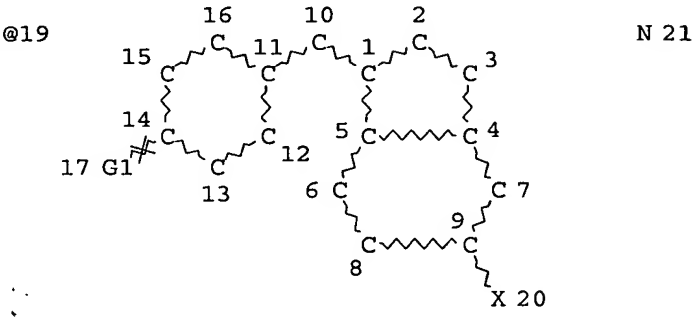
S 23

VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18

NSPEC IS RC AT 19
NSPEC IS RC AT 21
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
L30 0 SEA FILE=BEILSTEIN SSS FUL L29
L31 STR



Se 23

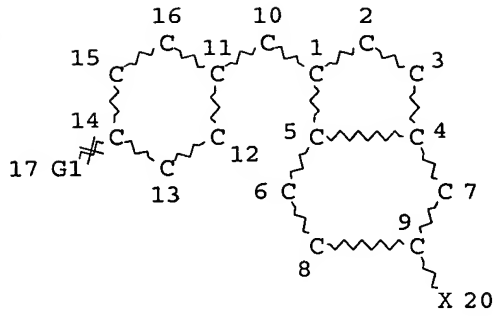
VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 21
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
L32 0 SEA FILE=BEILSTEIN SSS FUL L31
L33 0 SEA FILE=BEILSTEIN ABB=ON PLU=ON L30 OR L32

=> => d que stat l37
L35 STR

S @18 Se @19



N 21

VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 21
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

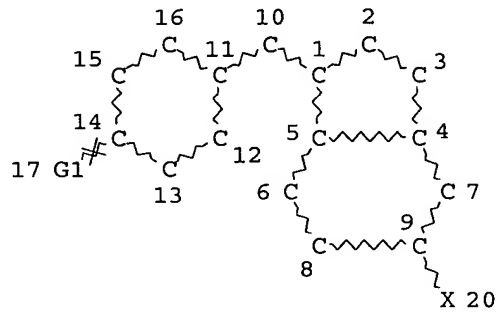
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE
L37 31 SEA FILE=WPIX SSS FUL L35

100.0% PROCESSED 570 ITERATIONS 31 ANSWERS
SEARCH TIME: 00.00.06

=> => d que stat l41
L35 STR

S @18 Se @19



N 21

VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 21
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 21

```
STEREO ATTRIBUTES: NONE
L41           1 SEA FILE=CHEMINFORMRX SSS FUL L35 (     2 REACTIONS)

100.0% DONE     452 VERIFIED       2 HIT RXNS                        1 DOCS
SEARCH TIME: 00.00.16


=> => d his ful

     (FILE 'HOME' ENTERED AT 15:42:50 ON 24 MAR 2006)

     FILE 'LREGISTRY' ENTERED AT 15:43:28 ON 24 MAR 2006

     FILE 'ZCAPLUS' ENTERED AT 15:43:53 ON 24 MAR 2006
               E US2003-723809/APPS

     FILE 'HCAPLUS' ENTERED AT 15:44:13 ON 24 MAR 2006
L1             1 SEA ABB=ON  PLU=ON  US2003-723809/APPS
               SAVE TEMP L1 VAL809HCAAPP/A

     FILE 'STNGUIDE' ENTERED AT 15:44:40 ON 24 MAR 2006

     FILE 'HCAPLUS' ENTERED AT 15:44:45 ON 24 MAR 2006
               D IBIB ED AB IND

     FILE 'STNGUIDE' ENTERED AT 15:44:45 ON 24 MAR 2006

     FILE 'STNGUIDE' ENTERED AT 15:44:49 ON 24 MAR 2006

     FILE 'WPIX' ENTERED AT 15:46:16 ON 24 MAR 2006
L2             1 SEA ABB=ON  PLU=ON  US2003-723809/APPS
               SAVE TEMP L2 VAL809WPIAPP/A

     FILE 'STNGUIDE' ENTERED AT 15:46:39 ON 24 MAR 2006

     FILE 'WPIX' ENTERED AT 15:46:46 ON 24 MAR 2006
               D IALL CODE

     FILE 'STNGUIDE' ENTERED AT 15:46:48 ON 24 MAR 2006

     FILE 'REGISTRY' ENTERED AT 15:47:23 ON 24 MAR 2006

     FILE 'HCAPLUS' ENTERED AT 15:47:27 ON 24 MAR 2006
L3             TRA L1 1- RN :       11 TERMS

     FILE 'REGISTRY' ENTERED AT 15:47:34 ON 24 MAR 2006
L4            11 SEA ABB=ON  PLU=ON  L3
               SAVE TEMP L4 VAL809REGAPP/A
               D SCAN

     FILE 'STNGUIDE' ENTERED AT 15:48:05 ON 24 MAR 2006

     FILE 'LREGISTRY' ENTERED AT 15:48:33 ON 24 MAR 2006
L5             STR

     FILE 'REGISTRY' ENTERED AT 15:54:54 ON 24 MAR 2006
L6            28 SEA SSS SAM L5
               D SCAN
```

```
     FILE 'STNGUIDE' ENTERED AT 15:55:59 ON 24 MAR 2006
                D QUE STAT

     FILE 'REGISTRY' ENTERED AT 15:57:42 ON 24 MAR 2006
L7            856 SEA SSS FUL L5
                  SAVE TEMP L7 VAL809PSET1/A
L8              7 SEA ABB=ON  PLU=ON  L4 NOT L7
                  D SCAN

     FILE 'STNGUIDE' ENTERED AT 15:58:40 ON 24 MAR 2006

     FILE 'HCAPLUS' ENTERED AT 16:00:46 ON 24 MAR 2006
L9           1798 SEA ABB=ON  PLU=ON  L7

     FILE 'STNGUIDE' ENTERED AT 16:00:53 ON 24 MAR 2006

     FILE 'LREGISTRY' ENTERED AT 16:00:55 ON 24 MAR 2006
L10               STR L5

     FILE 'REGISTRY' ENTERED AT 16:01:46 ON 24 MAR 2006
L11             33 SEA SUB=L7 SSS SAM L10
                  D QUE STAT
L12            622 SEA SUB=L7 SSS FUL L10
                  SAVE TEMP L12 VAL809RSET1/A

     FILE 'HCAPLUS' ENTERED AT 16:03:51 ON 24 MAR 2006
L13          1765 SEA ABB=ON  PLU=ON  L12
L14          1572 SEA ABB=ON  PLU=ON  L13 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
                  MY<2004 OR REVIEW/DT)

     FILE 'STNGUIDE' ENTERED AT 16:04:38 ON 24 MAR 2006

     FILE 'REGISTRY' ENTERED AT 16:05:40 ON 24 MAR 2006
L15             50 SEA ABB=ON  PLU=ON  L12 AND S>1
L16              0 SEA ABB=ON  PLU=ON  L12 AND SE>1
L17              0 SEA ABB=ON  PLU=ON  L12 AND S/ELS AND SE/ELS
L18             50 SEA ABB=ON  PLU=ON  (L15 OR L16 OR L17)
L19              8 SEA ABB=ON  PLU=ON  L4 NOT L18
                  D SCAN

     FILE 'STNGUIDE' ENTERED AT 16:07:17 ON 24 MAR 2006

     FILE 'REGISTRY' ENTERED AT 16:08:41 ON 24 MAR 2006
L20             29 SEA ABB=ON  PLU=ON  L18 AND N/ELS
                  D QUE STAT
L21              8 SEA ABB=ON  PLU=ON  L4 NOT L20
                  D SCAN

     FILE 'STNGUIDE' ENTERED AT 16:09:22 ON 24 MAR 2006

     FILE 'REGISTRY' ENTERED AT 16:10:31 ON 24 MAR 2006
                  SAVE TEMP L18 VAL809RSET2/A
                  SAVE TEMP L20 VAL809RSET3/A

     FILE 'STNGUIDE' ENTERED AT 16:11:25 ON 24 MAR 2006

     FILE 'REGISTRY' ENTERED AT 16:18:31 ON 24 MAR 2006

     FILE 'HCAPLUS' ENTERED AT 16:18:34 ON 24 MAR 2006
```

```
L22          20 SEA ABB=ON  PLU=ON  L20
L23          20 SEA ABB=ON  PLU=ON  L20 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
                MY<2004 OR REVIEW/DT)

     FILE 'STNGUIDE' ENTERED AT 16:19:12 ON 24 MAR 2006

     FILE 'REGISTRY' ENTERED AT 16:19:21 ON 24 MAR 2006
L24             ANALYZE PLU=ON  L20 1- LC :       8 TERMS
                D 1-8

     FILE 'HCAPLUS, USPATFULL, USPAT2, TOXCENTER, IFICDB, IFIPAT, IFIUDB'
     ENTERED AT 16:20:33 ON 24 MAR 2006
L25          69 SEA ABB=ON  PLU=ON  L20
L26          46 DUP REM L25 (23 DUPLICATES REMOVED)
                     ANSWERS '1-20' FROM FILE HCAPLUS
                     ANSWERS '21-43' FROM FILE USPATFULL
                     ANSWERS '44-45' FROM FILE TOXCENTER
                     ANSWER '46' FROM FILE IFICDB
L27          45 SEA ABB=ON  PLU=ON  L26 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
                MY<2004 OR REVIEW/DT)
L28          46 SEA ABB=ON  PLU=ON  L26 OR L27
                SAVE TEMP L28 VAL809MULS1/A

     FILE 'STNGUIDE' ENTERED AT 16:22:35 ON 24 MAR 2006
                D QUE STAT L7
                D QUE STAT L12
                D QUE STAT L18
                D QUE STAT L20
                D QUE STAT L24
                D L24 1-8
                D QUE STAT L28
                D QUE L20

     FILE 'BEILSTEIN' ENTERED AT 16:39:12 ON 24 MAR 2006
                D QUE L20
L29             STR L10
L30           0 SEA SSS FUL L29
L31             STR L29
L32           0 SEA SSS FUL L31
L33           0 SEA ABB=ON  PLU=ON  L30 OR L32
                SAVE TEMP L33 VAL809BEI1/A

     FILE 'STNGUIDE' ENTERED AT 16:44:00 ON 24 MAR 2006
                D QUE STAT L30
                D QUE STAT L32
                D QUE STAT L33

     FILE 'WPIX' ENTERED AT 16:45:39 ON 24 MAR 2006
                D QUE L20
L34           5 SEA SSS SAM L10
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 16:47:16 ON 24 MAR 2006

     FILE 'WPIX' ENTERED AT 16:47:38 ON 24 MAR 2006

     FILE 'LREGISTRY' ENTERED AT 16:48:10 ON 24 MAR 2006
                D QUE L20
L35             STR L10
```

```
     FILE 'WPIX' ENTERED AT 16:50:14 ON 24 MAR 2006
L36            1 SEA SSS SAM L35
                 D SCAN

     FILE 'STNGUIDE' ENTERED AT 16:50:52 ON 24 MAR 2006
                 D QUE STAT

     FILE 'WPIX' ENTERED AT 16:51:45 ON 24 MAR 2006
L37           31 SEA SSS FUL L35
                 SAVE TEMP L37 VAL809WPIS1/A

     FILE 'STNGUIDE' ENTERED AT 16:52:31 ON 24 MAR 2006
                 D QUE STAT L37

     FILE 'WPIX' ENTERED AT 16:53:33 ON 24 MAR 2006
L38           10 SEA ABB=ON  PLU=ON  L37/DCR
                 D TRI 1-10
L39            1 SEA ABB=ON  PLU=ON  L38 AND L2
                 SAVE TEMP L38 VAL809WPIS2/A

     FILE 'STNGUIDE' ENTERED AT 16:55:13 ON 24 MAR 2006

     FILE 'CHEMINFORMRX' ENTERED AT 16:55:25 ON 24 MAR 2006
                 D QUE L37
L40            0 SEA SSS SAM L35 (     0 REACTIONS)
                 D QUE STA
L41            1 SEA SSS FUL L35 (     2 REACTIONS)
                 SAVE TEMP L41 VAL809CHM1/A
                 D SCAN

     FILE 'STNGUIDE' ENTERED AT 16:57:01 ON 24 MAR 2006
                 D QUE STAT L41


     FILE HOME

     FILE LREGISTRY
     LREGISTRY IS A STATIC LEARNING FILE

     NEW CAS INFORMATION USE POLICIES, ENTER HELP USAGETERMS FOR DETAILS.

     FILE ZCAPLUS

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     FILE COVERS 1907 - 24 Mar 2006  VOL 144 ISS 14
     FILE LAST UPDATED: 23 Mar 2006  (20060323/ED)

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

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       substance identification.
```

FILE HCAPLUS

FILE COVERS 1907 - 24 Mar 2006 VOL 144 ISS 14
FILE LAST UPDATED: 23 Mar 2006 (20060323/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

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FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Mar 17, 2006 (20060317/UP).

FILE WPIX
FILE LAST UPDATED: 23 MAR 2006 <20060323/UP>
MOST RECENT DERWENT UPDATE: 200620 <200620/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE, PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

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http://scientific.thomson.com/support/patents/coverage/latestupdates/

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER GUIDES, PLEASE VISIT:
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FOR FURTHER DETAILS:
http://scientific.thomson.com/support/products/dwpifv/

>>> THE CPI AND EPI MANUAL CODES WILL BE REVISED FROM UPDATE 200601.
PLEASE CHECK:
http://scientific.thomson.com/support/patents/dwpiref/reftools/classificat

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 22 MAR 2006 HIGHEST RN 877759-05-2

DICTIONARY FILE UPDATES: 22 MAR 2006 HIGHEST RN 877759-05-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

```
**************************************************************
*                                                            *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                            *
**************************************************************
```

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 23 Mar 2006 (20060323/PD)
FILE LAST UPDATED: 23 Mar 2006 (20060323/ED)
HIGHEST GRANTED PATENT NUMBER: US7017190
HIGHEST APPLICATION PUBLICATION NUMBER: US2006064792
CA INDEXING IS CURRENT THROUGH 23 Mar 2006 (20060323/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Mar 2006 (20060323/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2006

FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 23 Mar 2006 (20060323/PD)
FILE LAST UPDATED: 23 Mar 2006 (20060323/ED)
HIGHEST GRANTED PATENT NUMBER: US2004103734
HIGHEST APPLICATION PUBLICATION NUMBER: US2006064553
CA INDEXING IS CURRENT THROUGH 23 Mar 2006 (20060323/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Mar 2006 (20060323/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2006

FILE TOXCENTER

FILE COVERS 1907 TO 21 Mar 2006 (20060321/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

The MEDLINE file segment has been updated with 2006 MEDLINE data and features. See HELP RLOAD for details.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.
See http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html
for a description of changes.

FILE IFICDB
FILE COVERS 1950 TO PATENT PUBLICATION DATE: 21 Mar 2006 (20060321/PD)
FILE LAST UPDATED: 22 Mar 2006 (20060322/ED)
HIGHEST GRANTED PATENT NUMBER: US7017190
HIGHEST APPLICATION PUBLICATION NUMBER: US2006059596
UNITERM INDEXING LAST UPDATED: 16 Mar 2006 (20060316/UP)
INDEXING CURRENT THROUGH PAT PUB DATE: 3 Jan 2006 (20060103/PD)

IFICDB reloaded on 9/22/05. Enter HELP RLOAD for details.

The (S) proximity operator should be used to correctly link chemical uniterms with role numbers. Enter 'HELP (S)' at an arrow prompt for more information on using the (S) operator when searching this file.

To ensure accurate searching using RANGE= or SET RANGE, enter HELP RANGE at an arrow promt (=>).

FILE IFIPAT
FILE COVERS 1950 TO PATENT PUBLICATION DATE: 21 Mar 2006 (20060321/PD)
FILE LAST UPDATED: 22 Mar 2006 (20060322/ED)
HIGHEST GRANTED PATENT NUMBER: US7017190
HIGHEST APPLICATION PUBLICATION NUMBER: US2006059596
UNITERM INDEXING IS AVAILABLE IN THE IFIUDB FILE
UNITERM INDEXING LAST UPDATED: 16 Mar 2006 (20060316/UP)
INDEXING CURRENT THROUGH PAT PUB DATE: 3 Jan 2006 (20060103/PD)

IFIPAT reloaded on 9/22/05. Enter HELP RLOAD for details.

FILE IFIUDB
FILE COVERS 1950 TO PATENT PUBLICATION DATE: 21 Mar 2006 (20060321/PD)
FILE LAST UPDATED: 22 Mar 2006 (20060322/ED)
HIGHEST GRANTED PATENT NUMBER: US7017190
HIGHEST APPLICATION PUBLICATION NUMBER: US2006059596
UNITERM INDEXING LAST UPDATED: 16 Mar 2006 (20060316/UP)
INDEXING CURRENT THROUGH PAT PUB DATE: 3 Jan 2006 (20060103/PDI)

IFIUDB reloaded on 9/22/05. Enter HELP RLOAD for details.

To ensure accurate searching using RANGE= or SET RANGE, enter HELP RANGE at an arrow promt (=>).

FILE BEILSTEIN
FILE LAST UPDATED ON MARCH 15, 2006

FILE COVERS 1771 TO 2006.
FILE CONTAINS 9,516,393 SUBSTANCES

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search

for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For mo detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

****
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST. *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS. *
* FOR PRICE INFORMATION SEE HELP COST *
****

NEW

*** PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.**

*** NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.**

FILE CHEMINFORMRX
FILE LAST UPDATED: 8 MAR 2006 <20060308/UP>

>>> CAS Registry Numbers are available for substances prior to 1995 <<<

=> => d his ful

(FILE 'HOME' ENTERED AT 09:12:24 ON 27 MAR 2006)

FILE 'HCAPLUS' ENTERED AT 09:12:34 ON 27 MAR 2006
ACT VAL809HCAAPP/A

L1 1 SEA ABB=ON PLU=ON US2003-723809/APPS

FILE 'WPIX' ENTERED AT 09:12:44 ON 27 MAR 2006
ACT VAL809WPIAPP/A

L2 1 SEA ABB=ON PLU=ON US2003-723809/APPS

FILE 'REGISTRY' ENTERED AT 09:13:00 ON 27 MAR 2006
ACT VAL809REGAPP/A

L3 (1)SEA ABB=ON PLU=ON US2003-723809/APPS
L4 SEL PLU=ON L3 1- RN : 11 TERMS
L5 11 SEA ABB=ON PLU=ON L4

ACT VAL809RSET3/A

L6 STR
L7 (856)SEA SSS FUL L6
L8 STR
L9 (622)SEA SUB=L7 SSS FUL L8
L10 (50)SEA ABB=ON PLU=ON L9 AND S>1
L11 (0)SEA ABB=ON PLU=ON L9 AND SE>1

```
L12 (         0)SEA ABB=ON  PLU=ON  L9 AND S/ELS AND SE/ELS
L13 (        50)SEA ABB=ON  PLU=ON  (L10 OR L11 OR L12)
L14          29 SEA ABB=ON  PLU=ON  L13 AND N/ELS
               ---------

     FILE 'HCAPLUS, USPATFULL, USPAT2, TOXCENTER, IFICDB, IFIPAT, IFIUDB'
     ENTERED AT 09:14:16 ON 27 MAR 2006
                ACT VAL809MULS1/A
               ---------
L15               STR
L16 (       856)SEA SSS FUL L15
L17               STR
L18 (       622)SEA SUB=L16 SSS FUL L17
L19 (        69)SEA ABB=ON  PLU=ON  L19
L20 (        46)DUP REM L19 (23 DUPLICATES REMOVED)
L21 (        20)SEA L20
L22 (        20)SEA L21 AND (AY<2004 OR PY<2004 OR PRY<2004 OR MY<2004 OR
                   REVIEW/DT)
L23 (        23)SEA L20
L24 (        22)SEA L23 AND (AY<2004 OR PY<2004 OR PRY<2004 OR MY<2004 OR
                   REVIEW/DT)
L25 (         0)SEA L20
L26 (         0)SEA L25 AND (AY<2004 OR PY<2004 OR PRY<2004 OR MY<2004 OR
                   REVIEW/DT)
L27 (         2)SEA L20
L28 (         2)SEA L27 AND (AY<2004 OR PY<2004 OR PRY<2004 OR MY<2004 OR
                   REVIEW/DT)
L29 (         1)SEA L20
L30 (         1)SEA L29 AND (AY<2004 OR PY<2004 OR PRY<2004 OR MY<2004 OR
                   REVIEW/DT)
L31 (         0)SEA L20
L32 (         0)SEA L31 AND (AY<2004 OR PY<2004 OR PRY<2004 OR MY<2004 OR
                   REVIEW/DT)
L33 (         0)SEA L20
L34 (         0)SEA L33 AND (AY<2004 OR PY<2004 OR PRY<2004 OR MY<2004 OR
                   REVIEW/DT)
L35 (        45)SEA ABB=ON  PLU=ON  L20 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
                   MY<2004 OR REVIEW/DT)
L36 (        20)SEA L20
L37          20 SEA L36 OR L22
L38 (        23)SEA L20
L39          23 SEA L38 OR L24
L40 (         0)SEA L20
L41 (         0)SEA L40 OR L26
L42 (         2)SEA L20
L43           2 SEA L42 OR L28
L44 (         1)SEA L20
L45           1 SEA L44 OR L30
L46 (         0)SEA L20
L47 (         0)SEA L46 OR L32
L48 (         0)SEA L20
L49 (         0)SEA L48 OR L34
L50          46 SEA ABB=ON  PLU=ON  L20 OR L35
               ---------

     FILE 'STNGUIDE' ENTERED AT 09:14:32 ON 27 MAR 2006

     FILE 'BEILSTEIN' ENTERED AT 09:14:41 ON 27 MAR 2006
                ACT VAL809BEI1/A
               ---------
```

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L51             STR
L52 (         0)SEA SSS FUL L51
L53             STR
L54 (         0)SEA SSS FUL L53
L55           0 SEA ABB=ON  PLU=ON  L52 OR L54
               ---------

     FILE 'CHEMINFORMRX' ENTERED AT 09:15:04 ON 27 MAR 2006
               ACT VAL809CHM1/A
              ---------
L56            STR
L57           1 SEA SSS FUL L56 (     2 REACTIONS)
               ---------
               D QUE

     FILE 'STNGUIDE' ENTERED AT 09:15:29 ON 27 MAR 2006

     FILE 'WPIX' ENTERED AT 09:15:40 ON 27 MAR 2006
               ACT VAL809WPIS1/A
              ---------
L58            STR
L59          31 SEA SSS FUL L58
               ---------
               ACT VAL809WPIS2/A
              ---------
L60            STR
L61 (        31)SEA SSS FUL L60
L62          10 SEA ABB=ON  PLU=ON  L61/DCR
               ---------

     FILE 'STNGUIDE' ENTERED AT 09:16:14 ON 27 MAR 2006

     FILE 'WPIX' ENTERED AT 09:17:51 ON 27 MAR 2006
               SELECT L2 1- DCRE
L63            8 SEA ABB=ON  PLU=ON  (917644-0-0-0/DCSE OR 917645-1-0-0/DCSE OR
                 917646-0-0-0/DCSE OR 917647-0-0-0/DCSE OR 917648-0-0-0/DCSE OR
                 917649-0-0-0/DCSE OR 917650-0-0-0/DCSE OR 917651-0-0-0/DCSE)
               D SCAN

     FILE 'STNGUIDE' ENTERED AT 09:18:31 ON 27 MAR 2006
               D QUE L59

     FILE 'WPIX' ENTERED AT 09:23:06 ON 27 MAR 2006
               SELECT L59 1- SDCN
L64          10 SEA ABB=ON  PLU=ON  (RADE8D/DCN OR RAD07D/DCN OR RAEL7G/DCN OR
                 RAEL7H/DCN OR RAEL7I/DCN OR RAIATA/DCN OR RAK8R3/DCN OR
                 RA0UIT/DCN OR RA0UIU/DCN OR RA0UJ9/DCN OR RA3O0J/DCN OR
                 RA5TOA/DCN OR RA5TOD/DCN OR RA5TOF/DCN OR RA5TOH/DCN OR
                 RA5TOI/DCN OR RA5TOJ/DCN OR RA5TOK/DCN OR RA5TO4/DCN OR
                 RA5TO5/DCN OR RA5TO6/DCN OR RA5TO7/DCN OR RA5TO8/DCN OR
                 RA7NPU/DCN OR RA7NPV/DCN OR RA7NPW/DCN OR RA7NPX/DCN OR
                 RA7NPY/DCN OR RA7NPZ/DCN OR RA7NQ0/DCN OR RA7NQ1/DCN)
L65          10 SEA ABB=ON  PLU=ON  L62 OR L64
               SAVE TEMP L65 VAL809WPIS3/A

     FILE 'STNGUIDE' ENTERED AT 09:24:12 ON 27 MAR 2006

     FILE 'ZCAPLUS' ENTERED AT 11:05:28 ON 27 MAR 2006
L66            QUE ABB=ON  PLU=ON  ?OXIDAS?
L67            QUE ABB=ON  PLU=ON  ?NEURODEGEN? OR (NEURO(1W)DEGEN?) OR
```

```
                (NEURON(3A)DEGEN?) OR ?ALZHEIM? OR ANTIALZHEIM? OR PARKINSON?
                OR ANTIPARKINSON? OR (AMYTROPH?(3A)?SCLER?) OR STROKE OR
                (HEART(1W)ATTACK) OR ?INFARCT? OR ?ISCHEM?
L68             QUE ABB=ON  PLU=ON  ?CARDIO? OR ?PULMON? OR ?VASCUL? OR
                ?CORONAR? OR ?CARDIAC? OR ?IMMUN? OR AUTOIMMUN? OR AGING OR
                AGE
L69             QUE ABB=ON  PLU=ON  MSRA OR MSRB OR (?METHIONIN?(5A)?REDUCTAS?)


     FILE 'WPIX' ENTERED AT 11:09:42 ON 27 MAR 2006
L70           9 SEA ABB=ON  PLU=ON  L65 AND ((?OXIDAS?/BIX) OR (?NEURODEGEN?/BI
                X OR (NEURO/BIX(1W)DEGEN?/BIX) OR (NEURON/BIX(3A)DEGEN?/BIX)
                OR ?ALZHEIM?/BIX OR ANTIALZHEIM?/BIX OR PARKINSON?/BIX OR
                ANTIPARKINSON?/BIX OR (AMYTROPH?/BIX(3A)?SCLER?/BIX) OR
                STROKE/BIX OR (HEART/BIX(1W)ATTACK/BIX) OR ?INFARCT?/BIX OR
                ?ISCHEM?/BIX) OR (?CARDIO?/BIX OR ?PULMON?/BIX OR ?VASCUL?/BIX
                OR ?CORONAR?/BIX OR ?CARDIAC?/BIX OR ?IMMUN?/BIX OR AUTOIMMUN?/
                BIX OR AGING/BIX OR AGE/BIX) OR (MSRA/BIX OR MSRB/BIX OR
                (?METHIONIN?/BIX(5A)?REDUCTAS?/BIX)))
L71           1 SEA ABB=ON  PLU=ON  L65 NOT L70

     FILE 'STNGUIDE' ENTERED AT 11:11:46 ON 27 MAR 2006

     FILE 'ZCAPLUS' ENTERED AT 11:12:42 ON 27 MAR 2006
L72             QUE ABB=ON  PLU=ON  WEISSBACH, H?/AU
L*** DEL        QUE BROT, N?/U
L73             QUE ABB=ON  PLU=ON  BROT, N?/AU

     FILE 'MEDLINE, BIOSIS, PASCAL, JICST-EPLUS, CABA, LIFESCI, EMBASE, DRUGU,
     DRUGB, VETU, VETB, SCISEARCH, CONF, CONFSCI, DISSABS' ENTERED AT 11:14:20
     ON 27 MAR 2006

     FILE 'REGISTRY' ENTERED AT 11:14:30 ON 27 MAR 2006
                SET SMARTSELECT ON
L74             SEL PLU=ON  L14 1- CHEM :      30 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, BIOSIS, PASCAL, JICST-EPLUS, CABA, LIFESCI, EMBASE, DRUGU,
     DRUGB, VETU, VETB, SCISEARCH, CONF, CONFSCI, DISSABS' ENTERED AT 11:14:33
     ON 27 MAR 2006
L75           0 SEA ABB=ON  PLU=ON  L74
                D QUE
                SAVE TEMP L75 VAL809MUL2S/A
L76        1382 SEA ABB=ON  PLU=ON  (L72 OR L73)
L77         389 SEA ABB=ON  PLU=ON  L76 AND (L66 OR L67 OR L68 OR L69)
L78          50 SEA ABB=ON  PLU=ON  L77 AND (FLA OR FLOR? OR FL)/SO,CS,PA
L79         188 SEA ABB=ON  PLU=ON  L77 AND (L66 OR L69)
L80          49 SEA ABB=ON  PLU=ON  L78 AND L79
L81          50 SEA ABB=ON  PLU=ON  L78 OR L80
                SAVE TEMP VAL809MUL2INV/A L81 VAL809MUL2IN/A

     FILE 'STNGUIDE' ENTERED AT 11:27:00 ON 27 MAR 2006

     FILE 'CHEMINFORMRX' ENTERED AT 11:29:52 ON 27 MAR 2006
L82           0 SEA ABB=ON  PLU=ON  L57 AND (L66 OR L67 OR L68 OR L69)

     FILE 'STNGUIDE' ENTERED AT 11:30:14 ON 27 MAR 2006

     FILE 'HCAPLUS, USPATFULL, USPAT2, TOXCENTER, IFICDB, IFIPAT, IFIUDB'
     ENTERED AT 11:32:24 ON 27 MAR 2006
```

```
L83           8 SEA ABB=ON  PLU=ON  L50 AND (L66/TI,IT,CC,CT,ST,STP OR
                L67/TI,IT,CC,CT,ST,STP OR L68/TI,IT,CC,CT,ST,STP OR L69/TI,IT,C
                C,CT,ST,STP)
L84          38 SEA ABB=ON  PLU=ON  L50 NOT L83

     FILE 'STNGUIDE' ENTERED AT 11:35:32 ON 27 MAR 2006

     FILE 'HCAPLUS, WPIX, TOXCENTER' ENTERED AT 11:35:55 ON 27 MAR 2006
L85         585 SEA ABB=ON  PLU=ON  (L72 OR L73)
L86          68 SEA ABB=ON  PLU=ON  L85 AND (?SULFID? OR ?SULFOX?)
L87          55 SEA ABB=ON  PLU=ON  L85 AND L69
L88           9 SEA ABB=ON  PLU=ON  (L86 OR L87) AND (FLOR? OR FLA OR FL)/SO,CS
                ,PA
                SAVE TEMP L88 VAL809MUL1IN/A

     FILE 'STNGUIDE' ENTERED AT 11:37:39 ON 27 MAR 2006
                D QUE STAT L83
                D QUE STAT L70

     FILE 'HCAPLUS, USPATFULL, WPIX' ENTERED AT 11:39:03 ON 27 MAR 2006
L89          15 DUP REM L83 L70 (2 DUPLICATES REMOVED)
                     ANSWERS '1-5' FROM FILE HCAPLUS
                     ANSWERS '6-8' FROM FILE USPATFULL
                     ANSWERS '9-15' FROM FILE WPIX

     FILE 'STNGUIDE' ENTERED AT 11:39:12 ON 27 MAR 2006

     FILE 'WPIX, HCAPLUS, USPATFULL' ENTERED AT 11:39:45 ON 27 MAR 2006
                D IBIB ED AB HITIND HITSTR

     FILE 'STNGUIDE' ENTERED AT 11:39:47 ON 27 MAR 2006

     FILE 'WPIX, HCAPLUS, USPATFULL' ENTERED AT 11:40:26 ON 27 MAR 2006
                D IBIB ED AB HITIND HITSTR 2-5

     FILE 'STNGUIDE' ENTERED AT 11:40:29 ON 27 MAR 2006

     FILE 'WPIX, HCAPLUS, USPATFULL' ENTERED AT 11:40:56 ON 27 MAR 2006
                D IBIB AB HITSTR 6-8

     FILE 'STNGUIDE' ENTERED AT 11:40:58 ON 27 MAR 2006

     FILE 'WPIX, HCAPLUS, USPATFULL' ENTERED AT 11:41:26 ON 27 MAR 2006
                D IALL ABEQ TECH ABEX HITSTR 9-15

     FILE 'STNGUIDE' ENTERED AT 11:41:33 ON 27 MAR 2006
                D QUE STAT L84
                D QUE STAT L55
                D QUE STAT L57
                D QUE STAT L71
                D QUE STAT L74
                D QUE STAT L75

     FILE 'HCAPLUS, USPATFULL, TOXCENTER, IFICDB, CHEMINFORMRX, WPIX' ENTERED
     AT 11:45:10 ON 27 MAR 2006
L90          40 DUP REM L84 L55 L57 L71 L75 (0 DUPLICATES REMOVED)
                     ANSWERS '1-15' FROM FILE HCAPLUS
                     ANSWERS '16-35' FROM FILE USPATFULL
                     ANSWERS '36-37' FROM FILE TOXCENTER
                     ANSWER '38' FROM FILE IFICDB
```

ANSWER '39' FROM FILE CHEMINFORMRX
ANSWER '40' FROM FILE WPIX

FILE 'STNGUIDE' ENTERED AT 11:45:17 ON 27 MAR 2006

FILE 'IFICDB' ENTERED AT 11:46:03 ON 27 MAR 2006

FILE 'STNGUIDE' ENTERED AT 11:46:30 ON 27 MAR 2006

FILE 'CHEMINFORMRX, WPIX, HCAPLUS, USPATFULL, TOXCENTER, IFICDB' ENTERED AT 11:46:45 ON 27 MAR 2006
D IBIB ED AB HITSTR

FILE 'STNGUIDE' ENTERED AT 11:46:46 ON 27 MAR 2006

FILE 'CHEMINFORMRX, WPIX, HCAPLUS, USPATFULL, TOXCENTER, IFICDB' ENTERED AT 11:47:10 ON 27 MAR 2006
D IBIB ED AB HITSTR 2-15

FILE 'STNGUIDE' ENTERED AT 11:47:16 ON 27 MAR 2006

FILE 'CHEMINFORMRX, WPIX, HCAPLUS, USPATFULL, TOXCENTER, IFICDB' ENTERED AT 11:47:49 ON 27 MAR 2006
D IBIB AB HITSTR 16-35

FILE 'STNGUIDE' ENTERED AT 11:47:56 ON 27 MAR 2006

FILE 'CHEMINFORMRX, WPIX, HCAPLUS, USPATFULL, TOXCENTER, IFICDB' ENTERED AT 11:48:28 ON 27 MAR 2006
D IBIB ED AB HITIND 36-37

FILE 'STNGUIDE' ENTERED AT 11:48:29 ON 27 MAR 2006

FILE 'CHEMINFORMRX, WPIX, HCAPLUS, USPATFULL, TOXCENTER, IFICDB' ENTERED AT 11:48:47 ON 27 MAR 2006
D IBIB AB 38

FILE 'STNGUIDE' ENTERED AT 11:48:48 ON 27 MAR 2006

FILE 'CHEMINFORMRX, WPIX, HCAPLUS, USPATFULL, TOXCENTER, IFICDB' ENTERED AT 11:49:07 ON 27 MAR 2006
D IBIB AB RX 39

FILE 'STNGUIDE' ENTERED AT 11:49:13 ON 27 MAR 2006

FILE 'CHEMINFORMRX, WPIX, HCAPLUS, USPATFULL, TOXCENTER, IFICDB' ENTERED AT 11:49:28 ON 27 MAR 2006
D IALL ABEQ TECH ABEX HITSTR 40

FILE 'STNGUIDE' ENTERED AT 11:49:31 ON 27 MAR 2006

FILE 'STNGUIDE' ENTERED AT 11:49:38 ON 27 MAR 2006
D QUE L88
D QUE L81

FILE 'HCAPLUS, WPIX, TOXCENTER, MEDLINE, BIOSIS, PASCAL, LIFESCI, EMBASE, DRUGU, SCISEARCH, CONFSCI' ENTERED AT 11:50:28 ON 27 MAR 2006
L91 28 DUP REM L88 L81 (31 DUPLICATES REMOVED)
ANSWERS '1-6' FROM FILE HCAPLUS
ANSWERS '7-8' FROM FILE TOXCENTER

ANSWERS '9-12' FROM FILE BIOSIS
ANSWER '13' FROM FILE DRUGU
ANSWERS '14-27' FROM FILE SCISEARCH
ANSWER '28' FROM FILE CONFSCI

FILE 'STNGUIDE' ENTERED AT 11:50:37 ON 27 MAR 2006

FILE 'BIOSIS, DRUGU, SCISEARCH, CONFSCI, HCAPLUS, TOXCENTER' ENTERED AT 11:50:47 ON 27 MAR 2006
D IBIB ED AB 1-28

FILE 'STNGUIDE' ENTERED AT 11:50:49 ON 27 MAR 2006

FILE 'STNGUIDE' ENTERED AT 11:51:16 ON 27 MAR 2006

FILE HOME

FILE HCAPLUS

FILE COVERS 1907 - 27 Mar 2006 VOL 144 ISS 14
FILE LAST UPDATED: 26 Mar 2006 (20060326/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE WPIX
FILE LAST UPDATED: 23 MAR 2006 <20060323/UP>
MOST RECENT DERWENT UPDATE: 200620 <200620/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE, PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomson.com/support/patents/coverage/latestupdates/

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER GUIDES, PLEASE VISIT:
http://scientific.thomson.com/support/products/dwpi/

>>> FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX FIRST VIEW - FILE WPIFV.
FOR FURTHER DETAILS:
http://scientific.thomson.com/support/products/dwpifv/

>>> THE CPI AND EPI MANUAL CODES WILL BE REVISED FROM UPDATE 200601.
PLEASE CHECK:
http://scientific.thomson.com/support/patents/dwpiref/reftools/classificat

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 26 MAR 2006 HIGHEST RN 878044-67-8
DICTIONARY FILE UPDATES: 26 MAR 2006 HIGHEST RN 878044-67-8

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 23 Mar 2006 (20060323/PD)
FILE LAST UPDATED: 23 Mar 2006 (20060323/ED)
HIGHEST GRANTED PATENT NUMBER: US7017190
HIGHEST APPLICATION PUBLICATION NUMBER: US2006064792
CA INDEXING IS CURRENT THROUGH 23 Mar 2006 (20060323/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Mar 2006 (20060323/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2006

FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 23 Mar 2006 (20060323/PD)
FILE LAST UPDATED: 23 Mar 2006 (20060323/ED)
HIGHEST GRANTED PATENT NUMBER: US2004103734
HIGHEST APPLICATION PUBLICATION NUMBER: US2006064553
CA INDEXING IS CURRENT THROUGH 23 Mar 2006 (20060323/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Mar 2006 (20060323/PD)

REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2006

FILE TOXCENTER

FILE COVERS 1907 TO 21 Mar 2006 (20060321/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

The MEDLINE file segment has been updated with 2006 MEDLINE data and features. See HELP RLOAD for details.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.
See http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html
for a description of changes.

FILE IFICDB
FILE COVERS 1950 TO PATENT PUBLICATION DATE: 23 Mar 2006 (20060323/PD)
FILE LAST UPDATED: 24 Mar 2006 (20060324/ED)
HIGHEST GRANTED PATENT NUMBER: US7017190
HIGHEST APPLICATION PUBLICATION NUMBER: US2006064792
UNITERM INDEXING LAST UPDATED: 16 Mar 2006 (20060316/UP)
INDEXING CURRENT THROUGH PAT PUB DATE: 3 Jan 2006 (20060103/PD)

IFICDB reloaded on 9/22/05. Enter HELP RLOAD for details.

The (S) proximity operator should be used to correctly link chemical uniterms with role numbers. Enter 'HELP (S)' at an arrow prompt for more information on using the (S) operator when searching this file.

To ensure accurate searching using RANGE= or SET RANGE,
enter HELP RANGE at an arrow promt (=>).

FILE IFIPAT
FILE COVERS 1950 TO PATENT PUBLICATION DATE: 23 Mar 2006 (20060323/PD)
FILE LAST UPDATED: 24 Mar 2006 (20060324/ED)
HIGHEST GRANTED PATENT NUMBER: US7017190
HIGHEST APPLICATION PUBLICATION NUMBER: US2006064792
UNITERM INDEXING IS AVAILABLE IN THE IFIUDB FILE
UNITERM INDEXING LAST UPDATED: 16 Mar 2006 (20060316/UP)
INDEXING CURRENT THROUGH PAT PUB DATE: 3 Jan 2006 (20060103/PD)

IFIPAT reloaded on 9/22/05. Enter HELP RLOAD for details.

FILE IFIUDB
FILE COVERS 1950 TO PATENT PUBLICATION DATE: 23 Mar 2006 (20060323/PD)
FILE LAST UPDATED: 24 Mar 2006 (20060324/ED)
HIGHEST GRANTED PATENT NUMBER: US7017190
HIGHEST APPLICATION PUBLICATION NUMBER: US2006064792
UNITERM INDEXING LAST UPDATED: 16 Mar 2006 (20060316/UP)
INDEXING CURRENT THROUGH PAT PUB DATE: 3 Jan 2006 (20060103/PDI)

IFIUDB reloaded on 9/22/05. Enter HELP RLOAD for details.

To ensure accurate searching using RANGE= or SET RANGE,

enter HELP RANGE at an arrow promt (=>).

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Mar 24, 2006 (20060324/UP).

FILE BEILSTEIN
FILE LAST UPDATED ON MARCH 15, 2006

FILE COVERS 1771 TO 2006.
FILE CONTAINS 9,516,393 SUBSTANCES

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For mo detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

****
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST. *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS. *
* FOR PRICE INFORMATION SEE HELP COST *
****

NEW
* **PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.**
* **NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.**

FILE CHEMINFORMRX
FILE LAST UPDATED: 8 MAR 2006 <20060308/UP>

>>> CAS Registry Numbers are available for substances prior to 1995 <<<

FILE ZCAPLUS

FILE COVERS 1907 - 27 Mar 2006 VOL 144 ISS 14
FILE LAST UPDATED: 26 Mar 2006 (20060326/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE MEDLINE
FILE LAST UPDATED: 25 MAR 2006 (20060325/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 22 March 2006 (20060322/ED)

FILE PASCAL
FILE LAST UPDATED: 27 MAR 2006 <20060327/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE IN THE BASIC INDEX (/BI) FIELD <<<

FILE JICST-EPLUS
FILE COVERS 1985 TO 20 MAR 2006 (20060320/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

FILE CABA
FILE COVERS 1973 TO 2 Mar 2006 (20060302/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

The CABA file was reloaded 7 December 2003. Enter HELP RLOAD for details.

FILE LIFESCI
FILE COVERS 1978 TO 20 Mar 2006 (20060320/ED)

FILE EMBASE
FILE COVERS 1974 TO 27 Mar 2006 (20060327/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

EMBASE is now updated daily. SDI frequency remains weekly (default) and biweekly.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE DRUGU
FILE LAST UPDATED: 20 MAR 2006 <20060320/UP>
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<
>>> THESAURUS AVAILABLE IN /CT <<<

FILE DRUGB
>>> FILE COVERS 1964 TO 1982 - CLOSED FILE <<<

FILE VETU
FILE LAST UPDATED: 02 JAN 2002 <20020102/UP>
FILE COVERS 1983-2001

FILE VETB
FILE LAST UPDATED: 25 SEP 94 <940925/UP>
FILE COVERS 1968-1982

FILE SCISEARCH

FILE COVERS 1974 TO 24 Mar 2006 (20060324/ED)

SCISEARCH has been reloaded, see HELP RLOAD for details.

FILE CONF
FILE LAST UPDATED: 23 DEC 2005 <20051223/UP>
FILE COVERS 1976 TO 2005.

<<< CONF IS NO LONGER BEING UPDATED AS OF JANUARY 2006 >>>

FILE CONFSCI
FILE COVERS 1973 TO 24 Mar 2006 (20060324/ED)

CSA has suspended updates until further notice.

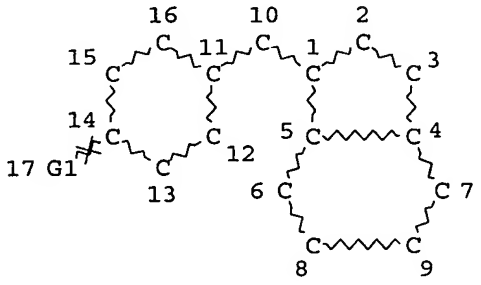
FILE DISSABS
FILE COVERS 1861 TO 24 FEB 2006 (20060224/ED)

=>

```
=> d his l83

     (FILE 'HCAPLUS, USPATFULL, USPAT2, TOXCENTER, IFICDB, IFIPAT, IFIUDB'
     ENTERED AT 11:32:24 ON 27 MAR 2006)
L83            8 S L50 AND (L66/TI,IT,CC,CT,ST,STP OR L67/TI,IT,CC,CT,ST,STP OR

=> d que stat l83
L15              STR
```



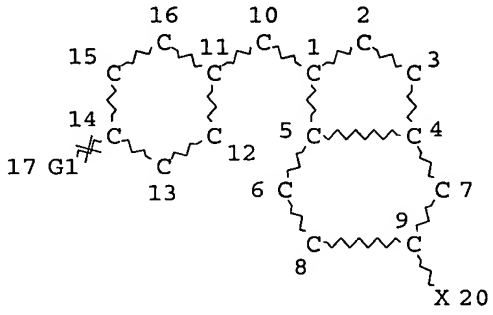
S @18 Se @19

```
VAR G1=18/19
NODE ATTRIBUTES:
NSPEC    IS RC      AT  18
NSPEC    IS RC      AT  19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  19

STEREO ATTRIBUTES: NONE
L16 (        856)SEA FILE=REGISTRY SSS FUL L15
L17              STR
```

S @18 Se @19




```
VAR G1=18/19
NODE ATTRIBUTES:
NSPEC    IS RC      AT  18
NSPEC    IS RC      AT  19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

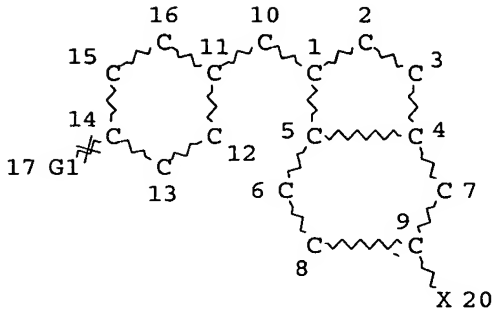
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  20

STEREO ATTRIBUTES: NONE
L18 (        622)SEA FILE=REGISTRY SUB=L16 SSS FUL L17
```

```
L19 (        69)SEA L19
L20 (        46)DUP REM L19 (23 DUPLICATES REMOVED)
L21 (        20)SEA FILE=HCAPLUS L20
L22 (        20)SEA FILE=HCAPLUS L21 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
                MY<2004 OR REVIEW/DT)
L23 (        23)SEA FILE=USPATFULL L20
L24 (        22)SEA FILE=USPATFULL L23 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
                MY<2004 OR REVIEW/DT)
L25 (         0)SEA FILE=USPAT2 L20
L26 (         0)SEA FILE=USPAT2 L25 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
                MY<2004 OR REVIEW/DT)
L27 (         2)SEA FILE=TOXCENTER L20
L28 (         2)SEA FILE=TOXCENTER L27 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
                MY<2004 OR REVIEW/DT)
L29 (         1)SEA FILE=IFICDB L20
L30 (         1)SEA FILE=IFICDB L29 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
                MY<2004 OR REVIEW/DT)
L31 (         0)SEA FILE=IFIPAT L20
L32 (         0)SEA FILE=IFIPAT L31 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
                MY<2004 OR REVIEW/DT)
L33 (         0)SEA FILE=IFIUDB L20
L34 (         0)SEA FILE=IFIUDB L33 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
                MY<2004 OR REVIEW/DT)
L35 (        45)SEA L20 AND (AY<2004 OR PY<2004 OR PRY<2004 OR MY<2004 OR
                REVIEW/DT)
L36 (        20)SEA FILE=HCAPLUS L20
L37          20 SEA FILE=HCAPLUS L36 OR L22
L38 (        23)SEA FILE=USPATFULL L20
L39          23 SEA FILE=USPATFULL L38 OR L24
L40 (         0)SEA FILE=USPAT2 L20
L41 (         0)SEA FILE=USPAT2 L40 OR L26
L42 (         2)SEA FILE=TOXCENTER L20
L43           2 SEA FILE=TOXCENTER L42 OR L28
L44 (         1)SEA FILE=IFICDB L20
L45           1 SEA FILE=IFICDB L44 OR L30
L46 (         0)SEA FILE=IFIPAT L20
L47 (         0)SEA FILE=IFIPAT L46 OR L32
L48 (         0)SEA FILE=IFIUDB L20
L49 (         0)SEA FILE=IFIUDB L48 OR L34
L50          46 SEA L20 OR L35
L66             QUE  ABB=ON  PLU=ON  ?OXIDAS?
L67             QUE  ABB=ON  PLU=ON  ?NEURODEGEN? OR (NEURO(1W)DEGEN?) OR
                 (NEURON(3A)DEGEN?) OR ?ALZHEIM? OR ANTIALZHEIM? OR PARKI
                NSON? OR ANTIPARKINSON? OR (AMYTROPH?(3A)?SCLER?) OR STRO
                KE OR (HEART(1W)ATTACK) OR ?INFARCT? OR ?ISCHEM?
L68             QUE  ABB=ON  PLU=ON  ?CARDIO? OR ?PULMON? OR ?VASCUL? OR
                ?CORONAR? OR ?CARDIAC? OR ?IMMUN? OR AUTOIMMUN? OR AGING
                OR AGE
L69             QUE  ABB=ON  PLU=ON  MSRA OR MSRB OR (?METHIONIN?(5A)?RED
                UCTAS?)
L83           8 SEA L50 AND (L66/TI,IT,CC,CT,ST,STP OR L67/TI,IT,CC,CT,ST,STP
                OR L68/TI,IT,CC,CT,ST,STP OR L69/TI,IT,CC,CT,ST,STP)


=> d que stat l70
L60             STR
```

S @18 Se @19



N 21

VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 21
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE
L61 (31) SEA FILE=WPIX SSS FUL L60
L62 10 SEA FILE=WPIX ABB=ON PLU=ON L61/DCR
L64 10 SEA FILE=WPIX ABB=ON PLU=ON (RADE8D/DCN OR RAD07D/DCN OR RAEL7G/DCN OR RAEL7H/DCN OR RAEL7I/DCN OR RAIATA/DCN OR RAK8R3/DCN OR RA0UIT/DCN OR RA0UIU/DCN OR RA0UJ9/DCN OR RA300J/DCN OR RA5TOA/DCN OR RA5TOD/DCN OR RA5TOF/DCN OR RA5TOH/DCN OR RA5TOI/DCN OR RA5TOJ/DCN OR RA5TOK/DCN OR RA5TO4/DCN OR RA5TO5/DCN OR RA5TO6/DCN OR RA5TO7/DCN OR RA5TO8/DCN OR RA7NPU/DCN OR RA7NPV/DCN OR RA7NPW/DCN OR RA7NPX/DCN OR RA7NPY/DCN OR RA7NPZ/DCN OR RA7NQ0/DCN OR RA7NQ1/DCN)
L65 10 SEA FILE=WPIX ABB=ON PLU=ON L62 OR L64
L70 9 SEA FILE=WPIX ABB=ON PLU=ON L65 AND ((?OXIDAS?/BIX) OR (?NEURODEGEN?/BIX OR (NEURO/BIX(1W)DEGEN?/BIX) OR (NEURON/BIX(3A)DEGEN?/BIX) OR ?ALZHEIM?/BIX OR ANTIALZHEIM?/BIX OR PARKINSON?/BIX OR ANTIPARKINSON?/BIX OR (AMYTROPH?/BIX(3A)?SCLER?/BIX) OR STROKE/BIX OR (HEART/BIX(1W)ATTACK/BIX) OR ?INFARCT?/BIX OR ?ISCHEM?/BIX) OR (?CARDIO?/BIX OR ?PULMON?/BIX OR ?VASCUL?/BIX OR ?CORONAR?/BIX OR ?CARDIAC?/BIX OR ?IMMUN?/BIX OR AUTOIMMUN?/BIX OR AGING/BIX OR AGE/BIX) OR (MSRA/BIX OR MSRB/BIX OR (?METHIONIN?/BIX(5A)?REDUCTAS?/BIX)))

=> dup rem l83 l70
FILE 'HCAPLUS' ENTERED AT 11:39:03 ON 27 MAR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPATFULL' ENTERED AT 11:39:03 ON 27 MAR 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'WPIX' ENTERED AT 11:39:03 ON 27 MAR 2006

```
COPYRIGHT (C) 2006 THE THOMSON CORPORATION
PROCESSING COMPLETED FOR L83
PROCESSING COMPLETED FOR L70
L89          15 DUP REM L83 L70 (2 DUPLICATES REMOVED)
                ANSWERS '1-5' FROM FILE HCAPLUS
                ANSWERS '6-8' FROM FILE USPATFULL
                ANSWERS '9-15' FROM FILE WPIX

=> file stnguide
FILE 'STNGUIDE' ENTERED AT 11:39:12 ON 27 MAR 2006
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Mar 24, 2006 (20060324/UP).
```

```
=> d ibib ed ab hitind hitstr
YOU HAVE REQUESTED DATA FROM FILE 'WPIX, HCAPLUS, USPATFULL' - CONTINUE? (Y)/N:y


L89  ANSWER 1 OF 15  HCAPLUS  COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2005:547257  HCAPLUS
DOCUMENT NUMBER:          143:77866
TITLE:                    Preparation of nitrate esters having a β- or
                          γ-sufur atom for protection of cells/tissues
                          from oxidative damage.
INVENTOR(S):              Thatcher, Gregory R. j.; Bennett, Brian M.; Reynolds,
                          James N.; Boegman, Roland J.; Jhamandas, Khem
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 83 pp., Cont.-in-part of U.S.
                          Ser. No. 147,808.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   6
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     US 2005137191         A1    20050623    US 2004-943264          20040917 <--
     US 5807847            A     19980915    US 1996-658145          19960604 <--
     US 5883122            A     19990316    US 1997-867856          19970603 <--
     US 6310052            B1    20011030    US 1999-267379          19990315 <--
     EP 1518553            A2    20050330    EP 2004-28372           20001227 <--
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI, CY, TR
     US 2002177622         A1    20021128    US 2002-147808          20020520 <--
     US 6916835            B2    20050712
     WO 2006029532         A1    20060323    WO 2005-CA1417          20050916
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ,
             LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ,
             NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG,
             SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN,
             YU, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
             GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.:                    US 1996-658145      A2 19960604 <--
                                          US 1997-867856      A2 19970603 <--
                                          US 1999-267379      A3 19990315 <--
                                          US 1999-473713      A2 19991229 <--
                                          US 2002-147808      A2 20020520 <--
                                          EP 2000-986925      A3 20001227 <--
                                          US 2001-851591      A3 20010510 <--
                                          US 2002-108513      A3 20020329 <--
                                          US 2004-943264      A  20040917
OTHER SOURCE(S):          MARPAT 143:77866
ED   Entered STN:  24 Jun 2005
AB   YXCR3R4(CR17R18)n(CR1R2)mONO2 [m, n = 0-10; R3, R4, R17 = H, nitrate, A;
     R1 = H, A; A = (substituted) (unsatd.) (cyclic) aliphatyl; R1R3, R4R17 =
     aliphatyl linkage; R2, R18 = H, A, XY; X = F, Cl, Br, Cl, NO2, CH2, CF2,
```

O, NH, NMe, cyano, NHOH, N3, S, SCN, SO, SO2, etc.; Y = null, F, Cl, Br, Cl, Me, CF2H, CF3, OH, NH2, S, SCN, SH, etc.; with provisos], were prepared Thus, [O2NOCH2CH(ONO2)CH2S]2 (prepared via the corresponding Bunte salt) at 200 μmol/kg s.c. gave virtually complete protection against 6-OHDA killing of dopaminergic neurons in rats.

IC ICM A61K031-537
ICS A61K031-455; A61K031-381; C07D265-30; C07D339-02

INCL 514232200; 514509000; 514355000; 514406000; 514464000; 514440000; 514365000; 544162000; 546315000; 549020000

CC 23-21 (Aliphatic Compounds)
Section cross-reference(s): 1, 27, 28, 32, 33, 63

IT **Ischemia**
(cerebral, treatment of damage; preparation of nitrate esters having a β- or γ-sufur atom for protection of cells/tissues from oxidative damage)

IT Brain, disease
(cerebrovascular, cerebral **vascular** occlusion, treatment of damage; preparation of nitrate esters having a β- or γ-sufur atom for protection of cells/tissues from oxidative damage)

IT Heart, disease
(**infarction**, treatment of damage; preparation of nitrate esters having a β- or γ-sufur atom for protection of cells/tissues from oxidative damage)

IT Brain, disease
(**ischemia**, treatment of damage; preparation of nitrate esters having a β- or γ-sufur atom for protection of cells/tissues from oxidative damage)

IT Injury
(**pulmonary**, treatment of damage; preparation of nitrate esters having a β- or γ-sufur atom for protection of cells/tissues from oxidative damage)

IT Brain, disease
(**stroke**, treatment of damage; preparation of nitrate esters having a β- or γ-sufur atom for protection of cells/tissues from oxidative damage)

IT **Aging, animal**
Alcoholism
Alzheimer's disease
Anaphylaxis
Aneurysm
Anxiety
Asthma
Cachexia
Cataract
Cirrhosis
Cystic fibrosis
Dermatitis
Diabetes mellitus
Drug dependence
Eczema
Encephalomyelitis
Epilepsy
Eye, disease
Glaucoma (disease)
Hematopoietic neoplasm
Hepatitis
Hypoglycemia
Hypoxia
Ischemia
Lupus erythematosus

Meningitis
Multiple sclerosis
Mycosis
Obesity
Parkinson's disease
Psoriasis
Rheumatoid arthritis
Schizophrenia
Shock (circulatory collapse)
Ulcer
Urticaria
(treatment of damage; preparation of nitrate esters having a β- or γ-sufur atom for protection of cells/tissues from oxidative damage)

IT Blood vessel, disease
Inflammation
(**vasculitis**, treatment of damage; preparation of nitrate esters having a β- or γ-sufur atom for protection of cells/tissues from oxidative damage)

IT 349472-60-2P 349472-61-3P 349472-62-4P 349472-64-6P 349472-65-7P
349472-66-8P 349472-67-9P 349472-72-6P 349481-56-7P 349481-57-8P
349481-58-9P 349481-60-3P 349481-63-6P 349481-65-8P 349481-66-9P
349481-70-5P 349482-21-9P 349487-17-8P 349487-23-6P 349487-26-9P
349487-28-1P 349487-29-2P 349487-32-7P 349487-34-9P 854925-36-3P
854925-37-4P 854925-38-5P 854925-39-6P 854925-40-9P 854925-41-0P
854925-42-1P 854925-43-2P 854925-44-3P 854925-45-4P 854925-46-5P
854925-47-6P 854925-48-7P 854925-49-8P 854925-50-1P
854925-51-2P 854925-52-3P 854925-53-4P 854925-54-5P 854925-55-6P
854925-56-7P 854925-57-8P 854925-58-9P 854925-59-0P 854925-60-3P
854925-61-4P 854925-62-5P 854925-63-6P 854925-64-7P 854925-65-8P
854925-66-9P 854925-67-0P 854925-68-1P 854925-69-2P 854925-70-5P
854925-71-6P 854925-72-7P 854925-73-8P 854925-74-9P 854925-75-0P
854925-76-1P 854925-77-2P 854925-78-3P 854925-79-4P 854925-80-7P
854925-81-8P 854925-82-9P 854925-83-0P 854925-84-1P 854925-85-2P
854925-86-3P 854925-87-4P 854925-88-5P 854925-89-6P 854925-90-9P
854925-91-0P 854925-92-1P 854925-93-2P 854925-94-3P 854925-95-4P
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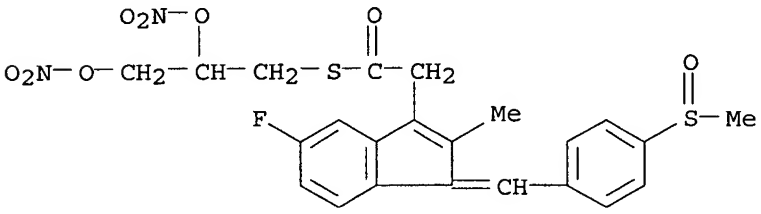
854926-01-5P 854926-02-6P 854926-03-7P 854926-04-8P 854926-05-9P
854926-06-0P 854926-07-1P 854926-08-2P 854926-09-3P 854926-10-6P
854926-11-7P 854926-12-8P 854926-13-9P 854926-14-0P 854926-15-1P
854926-16-2P 854926-17-3P 854926-18-4P 854926-19-5P 854926-20-8P
854926-21-9P 854926-22-0P 854926-23-1P 854926-24-2P 854926-25-3P
854926-26-4P 854926-27-5P 854926-28-6P 854926-29-7P 854926-30-0P
854926-31-1P 854926-32-2P 854926-33-3P 854926-34-4P 854926-35-5P
854926-36-6P 854926-37-7P 854926-38-8P 854926-39-9P 854926-40-2P
854926-41-3P 854926-42-4P 854926-43-5P 854926-44-6P 854926-45-7P
854926-46-8P 854926-47-9P 854926-48-0P 854926-49-1P 854926-50-4P
854926-58-2P 854926-59-3P 854926-60-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compound; preparation of nitrate esters having a β- or γ-sufur atom for protection of cells/tissues from oxidative damage)

IT **854925-47-6P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compound; preparation of nitrate esters having a β- or γ-sufur atom for protection of cells/tissues from oxidative

damage)
RN 854925-47-6 HCAPLUS
CN 1H-Indene-3-ethanethioic acid, 5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-, S-[2,3-bis(nitrooxy)propyl] ester (9CI) (CA INDEX NAME)



=> d ibib ed ab hitind hitstr 2-5
YOU HAVE REQUESTED DATA FROM FILE 'WPIX, HCAPLUS, USPATFULL' - CONTINUE? (Y)/N:y

L89 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:467703 HCAPLUS
DOCUMENT NUMBER: 141:28644
TITLE: Catalytic antioxidants and methods of use
INVENTOR(S): Weissbach, Herbert; Brot, Nathan
PATENT ASSIGNEE(S): Florida Atlantic University, USA; Hospital for Special Surgery
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PCT/US 03/38817

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004047772	A2	20040610	WO 2003-US38817	20031126 <--
WO 2004047772	A3	20040715		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004143016	A1	20040722	US 2003-723809	20031126 <--
PRIORITY APPLN. INFO.:			US 2002-429269P	P 20021126 <--

OTHER SOURCE(S): MARPAT 141:28644
ED Entered STN: 10 Jun 2004
AB The invention provides small mols. that act as catalytic antioxidants and methods of use thereof. The compds. can repeatedly bind and destroy reactive oxygen species by serving as substates for enzymes of the methionine sulfoxide reductase (Msr) class. Some embodiments of the

catalytic antioxidant compds. are derived from drugs with anti-inflammatory activity due to inhibition of cyclooxygenase enzymes.

IC ICM A61K

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

IT **Alzheimer's disease**
Anti-inflammatory agents
Parkinson's disease
(catalytic antioxidants and methods of use)

IT **Neuron**
(**degeneration**; catalytic antioxidants and methods of use)

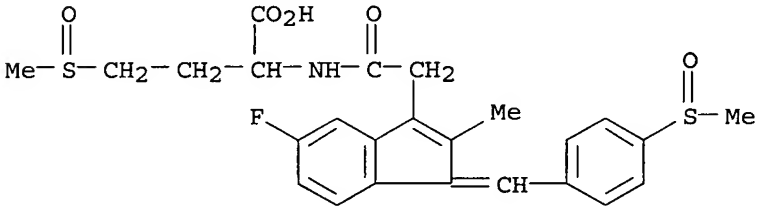
IT 70248-65-6, **Methionine** sulfoxide **reductase**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(catalytic antioxidants and methods of use)

IT 38194-50-2, Sulindac **700362-90-9 700362-91-0**
700362-92-1 700362-93-2 700362-94-3 700362-95-4
700362-96-5 700362-97-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(catalytic antioxidants and methods of use)

IT **700362-90-9 700362-91-0 700362-92-1**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(catalytic antioxidants and methods of use)

RN 700362-90-9 HCAPLUS

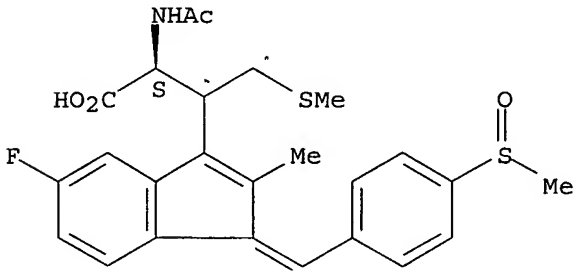
CN Butanoic acid, 2-[[[5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-inden-3-yl]acetyl]amino]-4-(methylsulfinyl)- (9CI) (CA INDEX NAME)



RN 700362-91-0 HCAPLUS

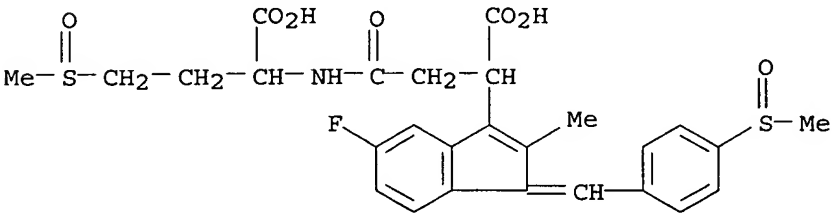
CN 1H-Indene-3-propanoic acid, α-(acetylamino)-5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-β-[(methylthio)methyl]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



Claim 3

RN 700362-92-1 HCAPLUS
CN 1H-Indene-3-acetic acid, α-[2-[[1-carboxy-3-(methylsulfinyl)propyl]amino]-2-oxoethyl]-5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]- (9CI) (CA INDEX NAME)



L89 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:523426 HCAPLUS
DOCUMENT NUMBER: 143:59971
TITLE: Preparation of pyrazole/isoxazole derivatives as substrates for **methionine** S-oxide **reductase**
INVENTOR(S): Connelly, Patrick R.; Connelly, Gregory P.; Magee, Andrew S.
PATENT ASSIGNEE(S): Synchrony Biosciences, Inc., USA
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
√	WO 2005054204	A2	20050616	WO 2004-US39597	20041124 <--
	WO 2005054204	A3	20050915		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2006014813	A1	20060119	US 2004-997752	20041124 <--
PRIORITY APPLN. INFO.:				US 2003-525209P	P 20031126 <--

OTHER SOURCE(S): MARPAT 143:59971
ED Entered STN: 17 Jun 2005
AB R1-A-X-B(-R3)-X-D-R2 [I; A = (hetero)aryl; B = heterocyclyl, carbocyclyl, etc.; D = heterocyclyl, carbocyclyl, etc.; X = bond, CO, CH2, etc.; R1-3 = H, Me, etc.] reacts with and neutralizes a reactive oxygen species, such as a free oxygen radical and can be regenerated to their original reactive chemical form by a naturally occurring enzyme. For instance, II is prepared in 5 steps from di-Me oxalate, 4-(methylsulfanyl)acetophenone, 4-hydrazinobenzenesulfonamide•HCl and methionine Me ester•HCl. I are useful to treat diseases in a patient characterized by a reactive

oxygen species. Furthermore, because these compds. can be regenerated back to their original, reactive chemical state in vivo, a single mol. can neutralize multiple mols. of the reactive species. This allows for the use of lower dosages for the treatment of disease, as compared to compds. presently used to treat that same disease, thus avoiding side effects associated with higher dosages.

IC ICM C07D231-12
ICS C07D231-14; C07D307-58; C07D275-02; C07D261-08; A61K031-415; A61K031-34; A61K031-42; A61P039-06

CC 28-8 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

ST pyrazole isoxazole msr **reductase** inhibitor reactive oxygen species prepn

IT Nervous system, disease
(degeneration; preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

IT Heart, disease
(**infarction**; preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

IT Reperfusion
(injury; preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

IT Analgesics
Anti-inflammatory agents
Antioxidants
Antitumor agents
Artery, disease
Cardiovascular agents
Eye, disease
Gingiva, disease
Heart, disease
Human
Inflammation
Ischemia
Lung, disease
Neoplasm
Oxidative stress, biological
Pain
Reproduction disorders
Respiratory system, disease
Sickle cell anemia
(preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

IT Injury
(reperfusion; preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

IT Rheumatic diseases
(rheumatoid disease; preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

IT Brain, disease
(**stroke**; preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

IT 70248-65-6, **Methionine** S-oxide **reductase**
329900-75-6, COX-2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

IT 853931-14-3P 853931-15-4P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP

(Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

IT 162012-06-8P 853931-17-6P 853931-18-7P 853931-19-8P 853931-20-1P
853931-21-2P 853931-22-3P 853931-23-4P 853931-24-5P 853931-25-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

IT **700362-90-9**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

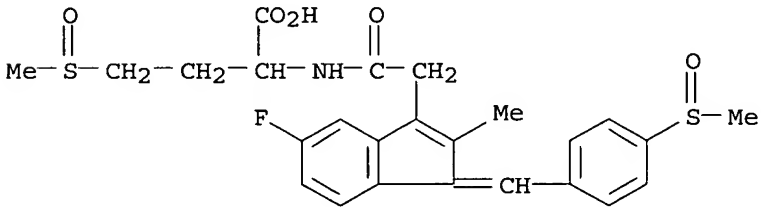
IT 553-90-2, Dimethyl oxalate 1778-09-2, 4-(Methylsulfanyl)acetophenone 2491-18-1, **Methionine** methyl ester hydrochloride 27918-19-0, 4-Hydrazinobenzenesulfonamide hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

IT 262851-25-2P 853931-16-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

IT **700362-90-9**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

RN 700362-90-9 HCAPLUS

CN Butanoic acid, 2-[[[5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-inden-3-yl]acetyl]amino]-4-(methylsulfinyl)- (9CI) (CA INDEX NAME)



L89 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:652131 HCAPLUS

DOCUMENT NUMBER: 139:214237

TITLE: Preparation of nitrate prodrugs able to release nitric oxide in a controlled and selective way and their use for prevention and treatment of inflammatory, **ischemic** and proliferative diseases

INVENTOR(S): Scaramuzzino, Giovanni

PATENT ASSIGNEE(S): Italy

SOURCE: Eur. Pat. Appl., 313 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1336602	A1	20030820	EP 2002-425075	20020213 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.: EP 2002-425075 20020213 <--

ED Entered STN: 21 Aug 2003

AB New pharmaceutical compds. of general formula F-(X)q (I) [q = 1-5, preferably 1; F is chosen among drugs such as δ-tocopherol, clidanac, diethylhomospermine, glucosamine, thymocartin, vofopitant, etc.; X is chosen among 4 groups M, T, V, and Y where M = ONO2, nitrate salt, nitrite ester, ONO, thoinitrite, SNO, etc., T = OR1-M, OR1OR1-M, SR1NR2R1-M, NR2R1-M, NR2R1SR1-M, etc., R1 = saturated or unsatd., linear or branched alkylene, having 1 to 21 carbon atoms or a saturated or unsatd., optionally heterosubstituted or branched cycloalkylene, having 3 to 7 carbon atoms or an optionally heterosubstituted arylene having 3 to 7 carbon atoms; R2 = H, saturated or unsatd., linear or branched 1-21 carbon atom alkyl, saturated or unsatd. optionally heterosubstituted or branched 3-7 carbon cycloalkyl, optionally heterosubstituted 3-7 carbon aryl; R1, R2 = OH, SH, F, Cl, Br, OPO3H2, CO2H, etc.; bond between F and T = carboxylic ester, carboxylic amide, glycoside, azo, thioester, sulfonic ester, etc.; V = Z-M2, OZ-M2, NR2Z-M2, R1Z-M2, OR1-M2, OR1Z-M2, M2 = M, R1-M, OR1-M, SR1-M, NR2R1-M; ZM2 = COCH2CH(M2)CH2N+Me3, COCH2CH2COM2, COCH(NHR2)CH2M2, etc.; Y = 4-COC6H4CH2ONO2, O(CH2)4ONO2, COCH(NH2)CH2ONO2, 3-OC6H4CH2ONO2, etc.] were prepared For example, α-tocopherol reacted with 4-HO2CC6H4CH2ONO2 to give the nitroxymethyl derivative II. The compds. of general formula I are nitrate prodrugs which can release nitric oxide in vivo in a controlled and selective way and without hypotensive side effects and for this reason they are useful for the preparation of medicines for prevention and treatment of inflammatory, ischemic, degenerative and proliferative diseases of musculoskeletal, tegumental, respiratory, gastrointestinal, genito-urinary and central nervous systems.

IC ICM C07C205-00
ICS A61K031-00

CC 26-1 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 1, 28, 29, 33, 34, 63

ST nitrate prodrug prepn; inflammation nitrate prodrug; **ischemia** nitrate prodrug; proliferative disease nitrate prodrug; degenerative disease nitrate prodrug; musculoskeletal disease nitrate prodrug; respiratory disease nitrate prodrug; gastrointestinal disease nitrate prodrug; genito urinary disease nitrate prodrug; central nervous system disease nitrate prodrug; tegumental disease nitrate prodrug

IT Inflammation
(Crohn's disease; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)

IT Intestine, disease
(Crohn's; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)

IT Bone, disease
(Paget's; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)

IT Respiratory distress syndrome
(adult; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative

diseases)
IT Prostate gland, disease
(benign hyperplasia; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Hyperplasia
(benign prostatic; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Bronchi, disease
Inflammation
(bronchitis; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Lung, disease
(chronic obstructive **pulmonary** disease; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Intestine, neoplasm
(colorectal; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Disease, animal
(degenerative; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Ulcer
(duodenal; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Intestine, disease
(duodenum, ulcer; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Invertebrate body covering
(epidermis; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Esophagus, disease
Inflammation
(esophagitis; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Intestine, neoplasm
(familial polyposis; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Inflammation
Stomach, disease
(gastritis; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Bladder, disease
(incontinence; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Muscle
(musculoskeletal diseases; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)

IT Hemoglobins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(nitrosylHbs; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Inflammation
Pancreas, disease
(pancreatitis; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Ulcer
(peptic; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Allergy
Alzheimer's disease
Anti-inflammatory agents
Anti-**ischemic** agents
Antitumor agents
Asthma
Bladder, neoplasm
Blood pressure
Brain, neoplasm
Central nervous system, disease
Cirrhosis
Cystic fibrosis
Dermatitis
Digestive tract, disease
Emphysema
Esophagus, neoplasm
Inflammation
Ischemia
Liver, neoplasm
Lung, neoplasm
Mammary gland, neoplasm
Multiple sclerosis
Osteoarthritis
Osteoporosis
Ovary, neoplasm
Pancreas, neoplasm
Prostate gland, neoplasm
Psoriasis
Reproductive system, disease
Respiratory system, disease
Rheumatoid arthritis
Sexual disorders
Skin, neoplasm
Stomach, neoplasm
Ulcer
Urinary system, disease
Uterus, neoplasm
(preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Drug delivery systems
(prodrugs; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Disease, animal
(proliferative; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative

diseases)
IT Inflammation
Prostate gland, disease
(prostatitis; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Inflammation
Nose, disease
(rhinitis; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Lupus erythematosus
(systemic; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Digestive tract, disease
(ulcer, peptic; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Inflammation
Intestine, disease
(ulcerative colitis; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT Biological transport
(uptake; preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT 55-63-0, Nitroglycerine 78-11-5, Pentaerythritol tetranitrate 87-33-2, Isosorbide dinitrate 14402-89-2, Sodium nitroprusside 16051-77-7, Isosorbide mononitrate 65141-46-0, Nicorandil 206197-03-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
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RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT 327610-87-7P 571186-50-0P 571186-51-1P 586347-27-5P 586347-30-0P 586347-40-2P 586347-41-3P 586347-44-6P
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT 50-23-7, Hydrocortisone
RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT 586347-24-2P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)
IT 13005-09-9P 96513-33-6P 116539-59-4P 198483-54-4P 257625-98-2P

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586350-05-2P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)

IT 586350-06-3P 586350-07-4P 586350-08-5P 586350-09-6P 586350-11-0P
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586388-35-4P 586388-39-8P 586388-42-3P 586388-45-6P 586388-46-7P
586388-47-8P 586388-48-9P 586388-49-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)

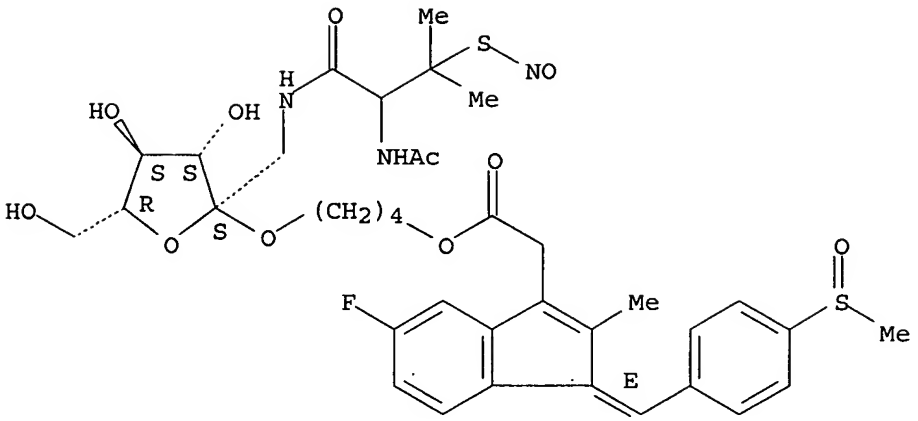
IT 50-02-2, Dexamethasone 50-24-8, Prednisolone 53-43-0, Prasterone 59-02-9, α-Tocopherol 66-84-2, D-Glucosamine hydrochloride 69-72-7, Salicylic acid, reactions 73-05-2, Phentolamine hydrochloride 83-88-5, Riboflavin, reactions 103-90-2, Acetaminophen 108-88-3, Toluene, reactions 117-39-5, Quercetin 128-13-2, Ursodiol 132-69-4, Benzydamine hydrochloride 620-24-6, 3-Hydroxybenzyl alcohol 876-08-4, 4-(Chloromethyl)benzoyl chloride 927-58-2, 4-Bromobutyryl chloride 2170-03-8, Itaconic anhydride 6232-88-8, 4-(Bromomethyl)benzoic acid 33036-62-3, 4-Bromobutan-1-ol 51333-22-3, Budesonide 56296-78-7, Fluoxetine hydrochloride 80573-04-2, Balsalazide 82413-20-5, Droloxifene 92340-57-3, 5-Hydroxyomeprazole 119169-78-7, Epristeride 131926-98-2, 5-Hydroxylansoprazole 136434-34-9, Duloxetine hydrochloride 151602-49-2, 5-O-Desmethylomeprazole 169590-42-5, Celecoxib 181695-72-7, Valdecoxib
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)

IT 19340-33-1P 101014-64-6P 101973-77-7P 116081-53-9P 116973-12-7P 132521-05-2P 190442-16-1P 258278-55-6P 571186-61-3P 586347-35-5P 586347-37-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)

IT **586348-19-8P 586350-91-6P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of nitrate prodrugs for treating or preventing inflammatory, **ischemic**, degenerative, and proliferative diseases)

RN 586348-19-8 HCAPLUS
CN α-D-Fructofuranoside, 4-[[[(1E)-5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-inden-3-yl]acetyl]oxy]butyl 1-[[2-(acetylamino)-3-methyl-3-(nitrosothio)-1-oxobutyl]amino]-1-deoxy- (9CI) (CA INDEX NAME)

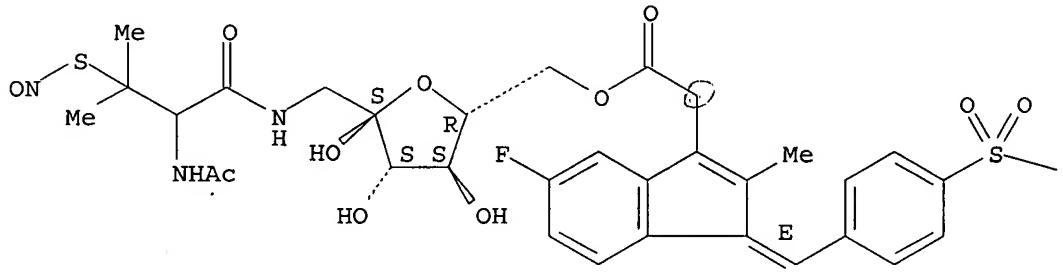
Absolute stereochemistry.
Double bond geometry as shown.



RN 586350-91-6 HCAPLUS
CN α-D-Fructofuranose, 1-[[2-(acetylamino)-3-methyl-3-(nitrosothio)-1-oxobutyl]amino]-1-deoxy-, 6-[(1E)-5-fluoro-2-methyl-1-[[4-(methylsulfonyl)phenyl]methylene]-1H-indene-3-acetate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:583274 HCAPLUS
DOCUMENT NUMBER: 115:183274
TITLE: Preparation of (arylalkyl)hydroxythiazoles as 5-lipoxygenase inhibitors

INVENTOR(S): Kerdesky, Francis A. J.; Brooks, Dee W.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9108744	A1	19910627	WO 1990-US6800	19901120 <--
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
US 5032588	A	19910716	US 1989-447756	19891208 <--
PRIORITY APPLN. INFO.:			US 1989-447756 A	19891208 <--

OTHER SOURCE(S): MARPAT 115:183274
ED Entered STN: 01 Nov 1991
AB Title compds. [I and II; R1 = (cyclo)alkyl, (substituted) (cyclo)alkenyl, aryl, arylalkyl, arylalkenyl, heterocyclyl, heterocyclylalkyl; M = H, pharmaceutically acceptable cation, acyl, silyl, etc.; Z = residue of nonsteroidal antiinflammatory drug] were prepared Thus, naproxen in CH2Cl2 at 5° was treated with (COCl)2 and cat. DMF; the mixture was allowed to warm to 23°, stirred 8 h, cooled to 5°, and treated with aqueous NH3 to give 85% amide, which was treated with Lawesson's reagent to give 33% thioamide. The latter in PhMe/pyridine was treated dropwise with α-chlorophenylacetyl chloride followed by 8 h reflux to give 27% I [R1 = Ph, M = H, Z = 1-(6-methoxy-2-naphthyl)ethyl]. I inhibited 5-lipoxygenase with IC50 = 0.06-0.9 μM.
IC ICM A61K031-54
ICS A61K031-44; A61K031-425; A61K031-41
CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
IT Allergy inhibitors
Cardiovascular agents
Nervous system agents
((arylalkyl)hydroxythiazoles)
IT 136690-82-9P 136690-83-0P 136690-84-1P 136690-85-2P 136690-86-3P
136690-87-4P 136690-88-5P 136690-89-6P 136690-90-9P 136690-91-0P
136690-92-1P 136690-93-2P 136690-94-3P 136690-95-4P 136690-96-5P
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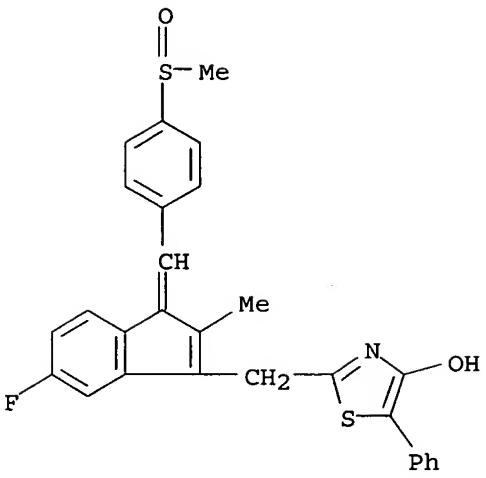
136691-22-0P 136691-23-1P 136691-24-2P 136691-25-3P
136691-26-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as lipoxygenase inhibitor)
IT **136691-26-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as lipoxygenase inhibitor)
RN 136691-26-4 HCAPLUS
CN 4-Thiazolol, 2-[[5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-inden-3-yl]methyl]-5-phenyl- (9CI) (CA INDEX NAME)



=> d ibib ab hitstr 6-8
YOU HAVE REQUESTED DATA FROM FILE 'WPIX, HCAPLUS, USPATFULL' - CONTINUE? (Y)/N:y

L89 ANSWER 6 OF 15 USPATFULL on STN
ACCESSION NUMBER: 2006:16426 USPATFULL
TITLE: Pharmaceutical compounds that regenerate in vivo
INVENTOR(S): Connelly, Patrick, Harvard, MA, UNITED STATES
Connelly, Gregory, Vienna, AUSTRIA
Magee, Andrew, Maynard, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2006014813	A1	20060119	
APPLICATION INFO.:	US 2004-997752	A1	20041124	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2003-525209P	20031126 (60)	<--

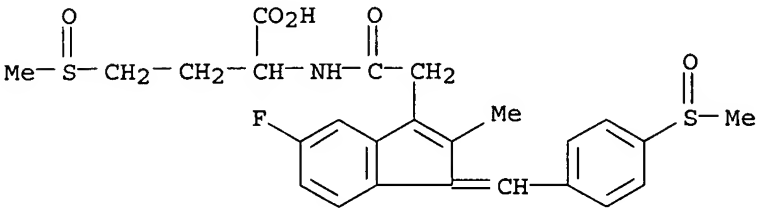
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: VERTEX PHARMACEUTICALS INC., 130 WAVERLY STREET, CAMBRIDGE, MA, 02139-4242, US
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 1815
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a class of compounds that reacts with and neutralizes a reactive oxygen species, such as a free oxygen radical, in a patient and which can then be regenerated back to their original reactive chemical form by a naturally occurring enzyme in said patient. These compounds are useful to treat diseases in a patient characterized by a reactive oxygen species. Moreover, because these compounds can be regenerated back to their original, reactive chemical state in vivo, a single molecule can neutralize multiple molecules of the reactive species. This allows for the use of lower dosages for the treatment of disease, as compared to compounds presently used to treat that same

disease, thus avoiding side effects associated with higher dosages.

IT **700362-90-9**
(preparation of pyrazole/isoxazole derivs. as substrates for **methionine** S-oxide **reductase**)

RN 700362-90-9 USPATFULL

CN Butanoic acid, 2-[[[5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-inden-3-yl]acetyl]amino]-4-(methylsulfinyl)- (9CI) (CA INDEX NAME)



L89 ANSWER 7 OF 15 USPATFULL on STN

ACCESSION NUMBER: 2004:185130 USPATFULL

TITLE: Catalytic antioxidants and methods of use

INVENTOR(S): Weissbach, Herbert, Boynton Beach, FL, UNITED STATES
Brot, Nathan, West Orange, NJ, UNITED STATES

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 2004143016	A1	20040722		
APPLICATION INFO.:	US 2003-723809	A1	20031126	(10)	<--

	NUMBER	DATE		
PRIORITY INFORMATION:	US 2002-429269P	20021126	(60)	<--

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: Stanley A. Kim, Ph.D., Esq., Akerman Senterfitt, Suite 400, 222 Lakeview Avenue, West Palm Beach, FL, 33401-6183

NUMBER OF CLAIMS: 28

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 13 Drawing Page(s)

LINE COUNT: 1362

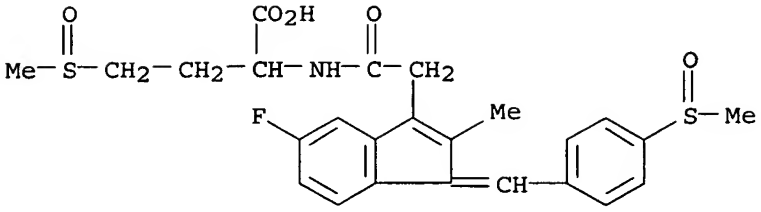
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides small molecules that act as catalytic antioxidants and methods of use thereof. The compounds can repeatedly bind and destroy reactive oxygen species by serving as substates for enzymes of the methionine sulfoxide reductase (Msr) class. Some embodiments of the catalytic antioxidant compounds are derived from drugs with anti-inflammatory activity due to inhibition of cyclooxygenase enzymes.

IT **700362-90-9 700362-91-0 700362-92-1**
(catalytic antioxidants and methods of use)

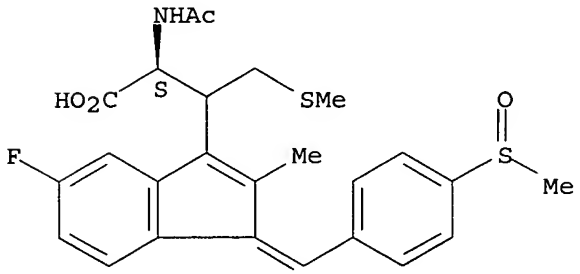
RN 700362-90-9 USPATFULL

CN Butanoic acid, 2-[[[5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-inden-3-yl]acetyl]amino]-4-(methylsulfinyl)- (9CI) (CA INDEX NAME)

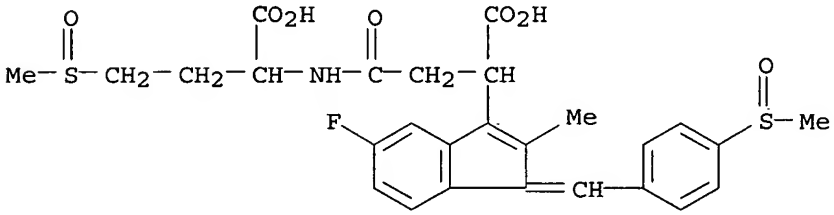


RN 700362-91-0 USPATFULL
CN 1H-Indene-3-propanoic acid, α-(acetylamino)-5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-β-[(methylthio)methyl]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 700362-92-1 USPATFULL
CN 1H-Indene-3-acetic acid, α-[2-[[1-carboxy-3-(methylsulfinyl)propyl]amino]-2-oxoethyl]-5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]- (9CI) (CA INDEX NAME)



L89 ANSWER 8 OF 15 USPATFULL on STN

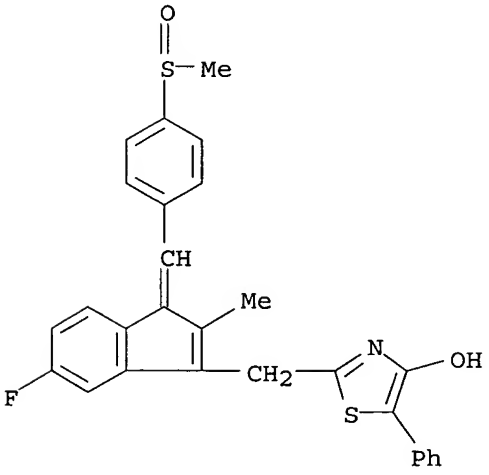
ACCESSION NUMBER:	91:56926 USPATFULL
TITLE:	Thiazole lipoxygenase-inhibiting compounds derived from non-steroidal antiinflammatory carboxylic acids
INVENTOR(S):	Brooks, Dee W., Libertyville, IL, United States Kerdesky, Francis A. J., Grayslake, IL, United States
PATENT ASSIGNEE(S):	Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 5032588		19910716		<--
APPLICATION INFO.:	US 1989-447756		19891208	(7)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shen, Cecilia
LEGAL REPRESENTATIVE: Janssen, Jerry F., Danckers, Andreas M., Weinstock, Steven F.
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1,5,6
LINE COUNT: 1176
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds of the formulae: ##STR1## and pharmaceutically acceptable salts, esters and prodrugs thereof, wherein M and R.sub.1 are independently selected from among optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, arylalkenyl, reduced heteroaryl and reduced heteroarylalkyl groups, and

Z is the residue of a compound selected from the class of compounds known as non-steroidal antiinflammatory grugs containing a carboxylic acid group, of the general form Z-COOH.

IT **136691-26-4P**
(preparation of, as lipoxygenase inhibitor)
RN 136691-26-4 USPATFULL
CN 4-Thiazolol, 2-[[5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-inden-3-yl]methyl]-5-phenyl- (9CI) (CA INDEX NAME)



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YOU HAVE REQUESTED DATA FROM FILE 'WPIX, HCAPLUS, USPATFULL' - CONTINUE? (Y)/N:y

L89 ANSWER 9 OF 15 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-794592 [81] WPIX
DOC. NO. CPI: C2005-244949
TITLE: New indole acetic acids and indene acetic acids, are cyclooxygenase inhibitors used to treat e.g. cancer and **neurodegenerative** diseases.
DERWENT CLASS: B02 B05 C02 C03
INVENTOR(S): FELTS, A S; JI, C; MARNETT, L J; PRUSAKIEWICZ, J J
PATENT ASSIGNEE(S): (UYVA-N) UNIV VANDERBILT

COUNTRY COUNT: 110
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2005250839	A1	20051110	(200581)*		63	A61K031-405
WO 2005112921	A2	20051201	(200581)	EN		A61K031-405

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2005250839	A1 Provisional	US 2004-565489P	20040426
		US 2005-114921	20050426
WO 2005112921	A2	WO 2005-US14328	20050426

PRIORITY APPLN. INFO: US 2004-565489P 20040426; US 2005-114921 20050426
INT. PATENT CLASSIF.:
MAIN: A61K031-405
BASIC ABSTRACT:

US2005250839 A UPAB: 20060227

NOVELTY - Indole acetic acid (I) and its derivatives are new.

DETAILED DESCRIPTION - Indole acetic acids and indene acetic acids of formula (I), and their derivatives, are new.

R1, R2 = H, halo, CF3, SCH3, SOCH3, SO2CH3, SO2NH2, 1-6C alkyl, branched alkyl, substituted alkyl, 1-6C alkoxy, branched alkoxy, substituted alkoxy, 1-6C alkylcarboxylic acid, branched alkylcarboxylic acid, substituted alkylcarboxylic acid or CH2N3 (where R2 is also CONH2 or benzyloxy);

R3, R4 = H, halo, CF3, 1-6C alkyl, branched alkyl, substituted alkyl, 1-6C alkoxy, branched alkoxy, substituted alkoxy, aryl, substituted aryl, benzyloxy, SCH3, SOCH3, SO2CH3 or SO2NH2;

R5 = H, 1-6C alkyl, branched alkyl, substituted alkyl or =O;

R6 = H, 1-6C alkyl, branched alkyl, substituted alkyl, 1-6C alkoxy, branched alkoxy, substituted alkoxy, benzyloxy, 1-6C alkylcarboxylic acid, branched alkylcarboxylic acid, substituted alkylcarboxylic acid or substituted octanone derivative (II) of formula CH3-CH2-(CH2)n-C(=O)-X-(R7)m-(Ar)s-(R8)t;

Ar = cyclohexyl or phenyl;

R7 = H, 1-6C alkyl, branched alkyl, substituted alkyl;

R8 = H, halo, 1-6C alkyl, branched alkyl, substituted alkyl, 1-6C alkoxy, branched alkoxy, substituted alkoxy, 1-6C alkylcarboxylic acid, branched alkylcarboxylic acid, substituted alkylcarboxylic acid, amino, nitro, CF3, bromoacetamidyl, benzoyl or 2-phenyl-oxiranyl;

X = O or NR9;

R9 = H or alkyl;

m, n, t = 05;

Y = H, halo, halo(methyl) (where one H of the methyl group is substituted with a halo); 2-6C alkyl, 2-6C branched alkyl or 2-6C substituted alkyl;

A = C or N; and
p, q = 0-4.

Provided the bond between the carbon bound to R5 and the indene ring is a single bond or a double bond and the six-membered ring (Z) to which R1 is bound is cyclohexyl or phenyl.

INDEPENDENT CLAIMS are also included for the following:

(1) a method for inhibiting growth of a cell, which comprises contacting the cell with (I), where (I) comprises a cyclooxygenase inhibitor comprising an indoleacetic/indenacetic acid functional group (having a 2' methyl group (A)) and the derivative lacks cyclooxygenase inhibitory activity as a result of modifying (A) to a moiety (hydrogen, halogen or halomethyl, where at least one hydrogen of the methyl group is substituted with a halogen; 2-6C (branched) alkyl, or 2-6C substituted alkyl;

(2) a method for modulating the activity of a peroxisome proliferator activated receptor (PPAR) isoform, which comprises contacting the PPAR isoform with (I); and

(3) a method for altering specificity of a cyclooxygenase inhibiting compound, which comprises providing (I) and replacing the 2' methyl group with a moiety.

ACTIVITY - Cytostatic; Antimetastatic; Neuroprotective; Nootropic; Antidiabetic.

MECHANISM OF ACTION - Tumor growth suppressor; Apoptosis inducer; Peroxisome proliferators activated receptor modulator; Cyclooxygenase inhibitor.

The ability of (I) to suppress the tumor growth was tested in human colorectal cancer cells. The results showed that the median effective dose of (I) was 0.04 mu M.

USE - Compounds (I) is useful to: inhibit the growth of a cell in a mammals; treat cancer, **neurodegenerative** disease (preferably **Alzheimer**'s disease) and diabetes; suppress tumor growth; and induce apoptosis in a cell (claimed). The treatment applies to humans and other mammals of importance due to being endangered (such as Siberian tigers), of economic importance (animals raised on farms for consumption by humans) and/or social importance (animals kept as pets or in zoos) to humans. Examples include carnivores other than humans (such as cats and dogs), swine (pigs, hogs, and wild boars), ruminants (such as cattle, oxen, sheep, giraffes, deer, goats, bison, and camels), and horses. The treatment also extends to birds, such as those that are endangered and those kept in zoos, as well as fowl (particularly domesticated fowl such as turkeys, chickens, ducks, geese and guinea fowl) as they are also of economic importance to humans.

ADVANTAGE - Compounds (I) causes less gastrointestinal toxicity (claimed).

Dwg.0/10

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-D01; B07-A03; B10-A08; B10-A10; B10-A16; B10-B02A; B10-C02; B10-C03; B10-C04; B10-D03; B10-G02; B10-G03; B10-H01; B10-H02; B10-J02; B14-C03; B14-D05C; B14-H01; B14-H03; B14-J01; B14-J01A4; B14-L01; B14-L06; B14-S04; C06-D01; C07-A03; C10-A08; C10-A10; C10-A16; C10-B02A; C10-C02; C10-C03; C10-C04; C10-D03; C10-G02; C10-G03; C10-H01; C10-H02; C10-J02; C14-C03; C14-D05C; C14-H01; C14-H03; C14-J01; C14-J01A4; C14-L01; C14-L06; C14-S04

TECH UPTX: 20060227

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: No general preparation given.

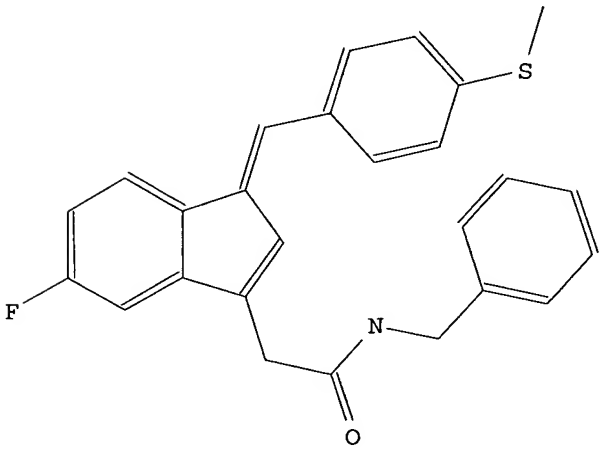
Preferred Components: The cyclooxygenase inhibitor comprises an indenacetic acid functional group and the moiety (hydrogen or fluorine). The cell (tumor/cancer cell) is in a subject (mammal preferably human). (I) is a non-steroidal anti-inflammatory drug (indomethacin, sulindac or their salts). The peroxisome proliferators activated receptor (PPAR) (present in a subject) isoform is PPARgamma. The cell is a cell in culture.
(I) is 2-des-methylindomethacin, eindenic acid sulfide (preferred), eindenic acid sulfoxide or eindenic acid sulfone.
Preferred Method: The method further comprises derivatizing the carboxylic acid moiety present on (I) to an ester or an amide, where the ester or amide (e.g. (1-(4-Chloro-benzoyl)-5-methoxy-1#H!-indol-3-yl)-acetic acid and N-benzyl-2- (6-fluoro-3- (4-methylsulfanyl-benzylidene)-3H-inden-1-yl)-acetamide .

ABEX UPTX: 20060227

SPECIFIC COMPOUNDS - 4 Compounds (I) are specifically claimed e.g. N-benzyl-2- (6-fluoro-3- (4-methylsulfanyl-benzylidene)-3H-inden-1-yl)-acetamide of formula (Ia).

ADMINISTRATION - Administration of (I) is intravenous, intrasynovial, transdermal, intramuscular, subcutaneous, topical, rectal, intravaginal, intratumoral, oral, buccal, nasal, parenteral, inhalation or insufflation. No dosage given.
EXAMPLE - 3-(4-Fluoro-phenyl)-propionic acid (5 g, 29.7 mmol) was added to polyphosphoric acid (65.4 g, 0.654 mol) at 50degreesC. The viscous mixture was heated at 90degreesC for 2 hours. The syrup was poured into ice water and stirred for 30 minutes. The aqueous mixture was extracted with ether and the combined organics were washed until neutralized. The resulting organic phase was worked up to afford 6-fluoro-indan-1-one as a yellow solid (2.06 g, 46%).
A solution of the indanone (2.06 g, 13.7 mmol) and ethyl bromoacetate (3.44 g, 20.6 mmol) in benzene (10 mL) was added over a 5 minute period to activated zinc (3.77 g, 57.7 mmol) in benzene (21 mL) and ether (10 mL). A few crystals of iodine were added to initiate the reaction and the mixture was held at reflux. At 3 hour intervals, 2 batches of zinc (1.8 g, 27.5 mmol) and ethyl bromoacetate (1.8 g, 10.8 mmol) were added and the mixture was refluxed overnight. The solution was cooled to room temperature and ethanol (5 mL) and acetic acid (23 mL) were added. The solution was poured into 1:1 aqueous acetic acid (100 mL) and the organic layer was separated. The aqueous phase was extracted and the combined organics were worked up to give crude (6-fluoro-1-hydroxy-indan-1-yl)-acetic acid ethyl ester (3.55 g).
The crude (6-Fluoro-1-hydroxyindan-1-yl)-acetic acid ethyl ester (3.55 g), p-toluene sulfonic acid.H2O (5.67 g, 29.8 mmol), and CaCl2 (4.13 g, 37.2 mmol) in toluene (66 mL) were refluxed overnight. The solution was filtered and the solid residue washed with benzene. The combined organics were washed with water, NaHCO3, water, dried (MgSO4), filtered, and concentrated in vacuo. Purification using flash chromatography afforded the title compound (6-fluoro-3H-inden-1-yl)-acetic acid ethyl ester as an orange solid (0.703 g).
To a solution of the (6-fluoro-3H-inden-1-yl)-acetic acid ethyl ester (0.668 g, 3.0 mmol) and p-methylthiobenzaldehyde (0.508 g, 3.3 mmol) in MeOH (18 mL) was added 1N NaOH (9 mL). The mixture was stirred at reflux for 2 hours. The solution was cooled, diluted with water, and extracted with ether. Residual ether was blown off the aqueous phase with nitrogen and the aqueous solution acidified with 50% acetic acid. The precipitated product was worked up to afford 6-fluoro-3-(4-methylsulfanyl-benzylidene)-3H-inden-1yl)-acetic acid (i.e. eidenic acid sulfide) as an orange solid (0.163 g, 17%).

DEFINITIONS - Preferred Definition:
R1 = 1-6C alkylcarboxylic acid or branched 1-6C alkylcarboxylic acid;
R2 = halo, 1-6C alkyl or branched alkyl, SCH3, SOCH3, SO2CH3 or SO2NH2;
R3-R5 and R7-R10 = H, 1-6C alkyl or branched alkyl or halo;
Rasterisk= singly or multiply substituted aryl, where the substituent is halo, NH2, OCH3, CF3, OH, 1-4C alkyl, branched alkyl, NO2, benzoyl, 2-phenyl-oxirane or NH-CO-CH2Br;
R12 = phenyl, phenyl-CH3, phenyl-COOH, phenyl-SCH3, phenyl-SOCH3, phenyl-SO2CH3, o-, m-, and/or p-halophenyl, phenyl-CH2N3 or 1-6C cycloalkyl; and
R11 = e.g. toluene, ethylbenzene, propylbenzene, butyl-benzene or benzyl-methyl-amine
DCSE 1190133-0-0-0
CN.S N-Benzyl-2-{6-fluoro-3-[1-(4-methylsulfanyl-phenyl)-methylidene]-3H-inden-1-yl}-acetamide
SDCN RAK8R3



L89 ANSWER 10 OF 15 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-110634 [12] WPIX
DOC. NO. CPI: C2006-039036
TITLE: New nitroxy derivatives are useful for the treatment of e.g. oxidative stress and endothelial dysfunction.
DERWENT CLASS: B05
INVENTOR(S): DEL SOLDATO, P
PATENT ASSIGNEE(S): (NICO-N) NICOX SA
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
AU 2005202824	A1	20050721	(200612)*		104	C07C219-14

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
AU 2005202824	A1	AU 2005-202824	20050628

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2005202824	A1 Div ex	AU 781643

PRIORITY APPLN. INFO: AU 2005-202824 20050628
INT. PATENT CLASSIF.:
MAIN: C07C219-14
SECONDARY: A61K031-21; C07C219-30; C07C229-42; C07C233-25; C07D219-10; C07D295-08; C07D309-30; C07D333-00; C07D401-12; C07D471-04; C07D495-00; C07D495-04; C07D499-68; C07H015-252

BASIC ABSTRACT:
AU2005202824 A UPAB: 20060217
NOVELTY - Nitroxy derivatives (I), or its salts are new.
DETAILED DESCRIPTION - Nitroxy derivatives of formula A-B-N(O)S (I), or its salts are new. (I) meets at least one of tests 1 - 3 e.g. test 1 (NEM) is a test in vivo carried out on four groups of rats (each formed by 10 rats), the controls (two groups) and the treated (two groups) of which .one group of the controls and one group of the treated respectively are administered with one dose of 25 mg/kg s.c. of N-ethyl maleimide (NEM) , the controls being treated with the carrier and the treated groups with the carrier + the drug of formula A = R-T1- wherein the free valence is Saturated as above indicated, administering the drug at a dose equivalent to the maximum one tolerated by the rats that did not receive NEM, i.e. the highest dose administrable to the animal at which there is no manifest toxicity, i.e. Such as to be symptomatologically observable; the drug complies with test 1, i.e. the drug can be used to prepare the compounds of general formula (I), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in the group treated with NEM + carrier + drug are observed gastrointestinal damages greater than those of the group treated with the carrier, or of the group treated with the carrier + drug, or of the group treated with the carrier + NEM;
provided that in formula (I) when X2 of B is a linear or branched 1-20C alkylene or a cycloalkylene having from 5 to 7 carbon atoms optionally Substituted, the drugs of formula A = R-T1 with the free valence Saturated as above described, used in the compound of formula (I), does not belong to the following classes: drugs for use in incontinence, antithrombotic drugs (ACE inhibitors), prostaglandins, antiinflammatory drugs (NSAIDS and corticosteroids) but not excluding antiinflammatory NSAIDS paracetamol and sundilac.
S = 2;
A = R-T1-;
R = a drug radical;
T1 = (CO)t or (X)t1;
X = O, S, NR1c, R1c or a free valence;
R1c = H or a linear or branched 1-6C alkyl;
t and t1 = 0 or 1;
B = -TB-X2-O-;
TB = (CO) or X;
X2 = bivalent radical.
Provided that i) t is 1 when t1 is 0 and t is 0 when t1 is 1; ii) TB is (CO) when t is 0 and TB is X when t1 is 0
ACTIVITY - Tranquillizer; Antiinflammatory; analgesic; Nootropic; Antidiabetic; Antibacterial; Virucide; Antiasthmatic; Mucolytic; Antilipemic; Cytostatic; Thrombolytic.
MECHANISM OF ACTION - Hemolysis inhibitor; DNA degradation inhibitor; apoptosis inhibitor.
USE - For preparation of drug for the treatment of inflammation associated with oxidative stress and endothelial dysfunction (claimed).
ADVANTAGE - The compounds have improved therapeutic index under

oxidative stress conditions.
Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B01-B03; B02-C03; B02-C04; B02-P03; B04-A04; B05-B01E; B05-B01G; B05-B01L; B05-B01N; B06-H; B07-H; B10-A05; B10-A09B; B10-A10; B10-A12C; B10-A15; B10-B01A; B10-B02A; B10-B02E; B10-B03B; B10-B04A; B10-C03; B10-C04B; B10-C04C; B10-C04E; B10-D02; B10-D03; B10-E02; B14-A01; B14-A02; B14-C01; B14-C03; B14-D03; B14-E08; B14-F02B1; B14-F04; B14-F06; B14-G02A; B14-H01; B14-H04; B14-J01A4; B14-J02A1; B14-J02B1; B14-J02D2; B14-L09; B14-N01; B14-S04; B14-S08

TECH UPTX: 20060217

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred compounds: The precursor drugs are Selected from anti-inflammatory drugs (e.g. aceclofenac, acematacin), analgesic drugs (e.g. acetaminophen, acetylsalicylic acid), bronchodilators and drugs active on the cholinergic system (e.g. acefylline, albuterol), expectorant-mucolytic drugs (e.g. ambroxol, bromhexine), antiasthmatic-antiallergic drugs, antihistaminic drugs (e.g. acrivastine), ACE-inhibitors (e.g. alacepril), beta-blockers (e.g. acebutolol), antithrombotic drugs and vasodilators (e.g. acetorphan), antidiabetic (e.g. acarbose), antitumoral (e.g. ancitabine), antiulcer drugs (e.g. arbaprostil), antihyperlipidemic drugs (e.g. atorvastatin), antibiotics (e.g. ampicillin), antiviral drugs (e.g. acyclovir), bone resorption inhibitors (e.g. alendronic acid) or antidementia drugs (e.g. oxiracetam). The precursor drugs are steroids (e.g. budesonide, hydrocortisone or algestone).

Preferred Tests: test 2 (CIP) is a test in vitro where human endothelial cells from the umbilical vein are harvested under Standard conditions, then divided into two groups (each group replicated five times), of which one is treated with a mixture of the drug 10-4 M concentration in the culture medium, the other group with the carrier; then cumene hydroperoxide (CIP) having a 5 mM concentration in the culture medium is added to each of the two groups; the drug meets test 2, i.e. the drug can be used to prepare the compounds of general formula (I), when a Statistically Significant inhibition of the apoptosis (cellular damage) induced by CIP is not obtained with p less than 0.01 with respect to the group treated with the carrier and CIP;

test 3 (L-NAME) is a test in vivo carried out on four groups of rats (each group formed by 10 rats) for 4 weeks and receiving drinking water, the controls (two groups) and the treated (two groups), of which one group of the controls and of the treated respectively receives in the above 4 weeks drinking water added of N-omega-nitro-L-arginine methyl ester (L-NAME) at a concentration of 400 mg/litre, the controls in the 4 weeks being administered with the carrier and the treated in the 4 weeks with the carrier + the drug, administering the carrier or the drug + carrier once a day, the drug being administered at the maximum dose tolerated by the group of rats not pretreated with L-NAME, i.e., the highest dose administrable to animals at which no manifest toxicity appears, i.e. Such as to be symptomatologically observable; after 4 weeks, the water Supply is Stopped for 24 hours and then Sacrificed, determining the blood pressure 1 hour before Sacrifice, and after Sacrifice of the rats determining the plasma glutamic pyruvic transaminase (GPT) after Sacrifice, and examining the gastric tissue; the drug meets test 3, i.e. the drug can be used to prepare the compounds of general formula (I), when in the group of rats treated with L-NAME + carrier + drug, greater hepatic damages (determined as higher values of GPT) and/or gastric and/or **cardiovascular** damages (determined as higher values of

blood-pressure) are found in comparison respectively with the group treated with the carrier alone, or with the group treated with the carrier + drug, or with the group treated with the carrier + L-NAME;
test 4A which must be met by the compound precursor of B is a test in vitro wherein a portion of an erythrocyte suspension formerly kept at 4 degrees C for 4 days, Said erythrocyte isolated by Standard procedures from Wistar male rats and Suspended in a physiological solution buffered at pH 7.4 with phosphate buffer, is centrifuged at 1000 rpm for 5 minutes and 0.1 ml of the centrifuged erythrocytes are diluted with Sodium phosphate buffer pH 7.4. at 50 ml; aliquots of 3,5 ml each (No.5 samples) are taken from Said diluted suspension and incubated at 37 degrees C in the presence of cumene hydroperoxide at a concentration 270 11M and the suspension turbidity determined at 710 nm at intervals of 30 minutes to establish the time (Tmax) at which occurs the maximum turbidity, that corresponds to the maximum amounts of cells lysed by cumene hydroperoxide (hemolysis assumed to be = 100%); then alcoholic solutions of the compounds precursors of B are added to 3.5 ml aliquots of the diluted suspension of centrifuged erythrocytes (tests carried out on 5 samples for each precursor of B assayed) in order to have a final concentration 2 mM of the precursor of B and then the resulting suspension pre-incubated for 30 minutes, cumene hydroperoxide is added in a quantity to have the Same above indicated final concentration and at Tmax is determined the percentage of hemolysis inhibition in the Sample from the ratio, multiplied by 100, between the absorbance of the Sample containing the erythrocytes, the precursor of B and cumene hydroperoxide respectively and that of the Sample containing the erythrocytes and cumene hydroperoxide; the precursors of B meet the test if they inhibit the hemolysis induced by cumene hydroperoxide by a percentage greater than 15%;
test 5 which must not be met by the precursor compound of B is an analytical determination carried out by adding aliquots of 10-4 M methanol solutions of the precursor of B or B1 or of C = -Tc-Y-H, having the free valence Saturated as above indicated, to a solution formed by mixing a 2 mM solution of deoxyribose in water with 100 mM of phosphate buffer and 1 mM of the salt Fe(NH4)2(SO4)2; after having thermostatted the solution at 37 degrees C for one hour, are added, in the order. aliquots of aqueous solutions of trichloroacetic acid 2.8% and of thiobarbituric acid 0.5 M, heating is effected at 100 degrees C for 15 minutes and the absorbance of the tested solutions is then read at 532 nm; the inhibition induced by the precursor of B or B1 or C = -Tc-Y-H in the confront of radical production by FE(II) is calculated as a percentage by means of the following formula: (1 - as/Ac)x 100 where as and Ac are respectively the absorbance values of the solution containing the tested compound and the iron salt and that of the solution containing only the iron salt; test 5 is met when the inhibition percentage as above defined of the B precursor is higher than or equal to 50%;

ABEX UPTX: 20060217

SPECIFIC COMPOUNDS - 11 compounds (I) are Specifically claimed, e.g. 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-(nitroxy)butyl ester (Ia).

ADMINISTRATION - Dosage is 5 - 25 mg/kg and is administered orally or parenterally (e.g. subcutaneously, intraperitoneally, intravenously or intramuscularly).

EXAMPLE - To a solution of 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-bromobutyl ester (2.72 g) in acetonitrile (25 ml) Silver nitrate (1.48 g) was added. The reaction mixture was heated at 80 degreeS C for 7 hours away from light, then cooled at room temperature, filtered and evaporated under reduced pressure. The residue was purified to yield 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-(nitroxy)butyl ester (Ia)

(56%).
DCSE 377182-0-0-0
CN.P NITROSULINDAC
CN.S [6-Fluoro-3-(4-methanesulfinyl-benzylidene)-2-methyl-3H-inden-1-yl]-acetic acid 4-nitrooxy-butyl ester
SDCN RA300J

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

L89 ANSWER 11 OF 15 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-203395 [19] WPIX
DOC. NO. CPI: C2004-080073
TITLE: New macrolide derivatives, useful for the treatment of inflammatory diseases of the lungs, joints, eyes, bowel, skin and heart, viral disease e.g. human **immuno** deficiency syndrome and neoplasia.
DERWENT CLASS: B01
INVENTOR(S): MARKOVIC, S; MERCEP, M; MESIC, M; TOMASKOVIC, L
PATENT ASSIGNEE(S): (PLIV) PLIVA DD; (PLIV) PLIVA ISTRAZIVACKI INST DOO; (PLIV) PLIVA DD ZAGREB
COUNTRY COUNT: 106
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2004005313	A2	20040115	(200419)*	EN	96	C07J000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW						
US 2004077612	A1	20040422	(200428)			A61K031-585
AU 2003264917	A1	20040123	(200459)			C07J000-00
NO 2005000575	A	20050315	(200540)			C07J043-00
EP 1551865	A2	20050713	(200546)	EN		C07K005-10
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR						
JP 2005538070	W	20051215	(200582)		78	C07K005-103
CN 1665831	A	20050907	(200607)			C07K005-10

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004005313	A2	WO 2003-IB3792	20030708
US 2004077612	A1 Provisional	US 2002-395190P	20020708
		US 2003-616046	20030708
AU 2003264917	A1	AU 2003-264917	20030708
NO 2005000575	A	WO 2003-IB3792	20030708
		NO 2005-575	20050202
EP 1551865	A2	EP 2003-762853	20030708
		WO 2003-IB3792	20030708
JP 2005538070	W	WO 2003-IB3792	20030708
		JP 2004-519131	20030708
CN 1665831	A	CN 2003-816097	20030708

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003264917	A1 Based on	WO 2004005313
EP 1551865	A2 Based on	WO 2004005313
JP 2005538070	W Based on	WO 2004005313

PRIORITY APPLN. INFO: US 2002-395190P 20020708; US 2003-616046 20030708

INT. PATENT CLASSIF.:

MAIN: A61K031-585; C07J000-00; C07J043-00; C07K005-10; C07K005-103

SECONDARY: A61K031-58; A61K047-48; A61P001-00; A61P001-04; A61P009-10; A61P011-00; A61P011-06; A61P011-08; A61P017-00; A61P017-04; A61P017-06; A61P019-02; A61P019-06; A61P021-00; A61P027-02; A61P029-00; A61P031-04; A61P031-12; A61P031-18; A61P035-00; A61P037-02; A61P037-08; A61P043-00; C07J017-00; C07K005-083

BASIC ABSTRACT:

WO2004005313 A UPAB: 20060302

NOVELTY - Macrolide derivatives (I), their salts, solvates and individual diastereoisomers are new.

DETAILED DESCRIPTION - Macrolide derivatives of formula (I), their salts, solvates and individual diastereoisomers are new.

M = a macrolide subunit possessing the property of accumulation in inflammatory cells;

V = anti-inflammatory steroid or non-steroidal subunit, an antineoplastic subunit or antiviral subunit; and

L = a linker molecule to which each of M and V are covalently linked.

An INDEPENDENT CLAIM is also included for the preparation of (I).

ACTIVITY - Antiinflammatory; **Immunosuppressive**; Respiratory-Gen.; Ophthalmological; Gastrointestinal-Gen.; Dermatological; Cardiant; Antiasthmatic; CNS-Gen.; Antiarthritic; Antirheumatic; Osteopathic; Antigout; Antiulcer; Antipsoriatic; Antibacterial; Cytostatic; Virucide; Anti-HIV.

Test details are described, but no results are given.

MECHANISM OF ACTION - None given.

USE - Compounds (I) are useful for the treatment of inflammatory diseases, disorders and conditions characterized by or associated with an undesirable inflammatory **immune** response, especially of diseases and conditions induced by or associated with an excessive secretion of tumor necrosis factor (TNF)- alpha and interleukin (IL-1).

Compounds (I) are useful for treating an inflammatory condition or an **immune** or anaphylactic disorder associated with infiltration of leukocytes into inflamed tissue e.g. inflammatory conditions or **immune** disorders of the lungs, joints, eyes, bowel, skin and heart (preferably asthma, adult respiratory distress syndrome, bronchitis, cystic fibrosis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, uveitis, conjunctivitis, inflammatory bowel conditions, Crohn's disease, ulcerative colitis, distal proctitis, psoriasis, eczema, dermatitis, **coronary infarct** damage, chronic inflammation, endotoxin shock and smooth muscle proliferation disorders).

Compounds (I) are also useful for abating inflammation in an affected organ or tissue, treatment of viral diseases, disorders and conditions (particularly HIV), for treating/abating a sign or symptom (preferably viral load, viral replication, viral activity, viremia, viral-specific

antigens, viral RNA, viral DNA, reverse transcriptase activity, antiviral cytoxic cell activity in the subject and T-cell or CD4+ cell count) or markers of a viral infection, treating neoplasia and its symptom, sign or marker (including tumor burden, tumor size, afflicted organ weight, tumor recurrence, survival time, length or extent of subject remission, growth of cancer cells, cancer cell survival, apoptosis index, metastasis extent or metastasis rate, a biological marker associated with a particular type of neoplasia, proliferation markers, activation of relevant oncogenes dysregulation of tumor associated receptor function, tumor-specific antigens and tumor associated angiogenesis). (All claimed.)
Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B01-B02; B02-D; B04-J02; B06-A03; B06-D01; B06-D04; B06-D09; B06-E05; B07-A01; B07-A02A; B07-B01; B07-D02; B07-D04C; B07-D12; B10-C03; B10-C04B; B10-C04C; B14-A01; B14-A02; B14-A02B1; B14-C02; B14-C03; B14-C06; B14-C09; B14-E10C; B14-F01; B14-F02F2; B14-G03; B14-H01; B14-H01B; B14-J01; B14-K01; B14-N01; B14-N03; B14-N17; B14-S06

TECH UPTX: 20040318

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The subunit V is derived from non-steroidal antiinflammatory drugs (NSAIDs) or antiviral compounds.

The linker molecule is peptide linker, comprising a polypeptide of 2-50 amino acids (preferably Gly-Phe-Leu, Gly-Gly-Phe, Gly-Phe-Phe, Gly-Phe-Gly, Gly-Leu-Gly, Gly-Val-Ala, Gly-Phe-Ala, Gly-Leu-Phe, Gly-Leu-Ala, Ala-Val-Ala, Gly-Gly-Phe-Leu, Gly-Phe-Leu-Gly, Gly-Phe-Ala-Leu, Ala-Leu-Ala-Leu, Gly-Phe-Phe-Leu, Gly-Leu-Leu-Gly, Gly-Phe-Tyr-Ala, Gly-Phe-Gly-Phe, Ala-Gly-Val-Phe, and Gly-Phe-Phe-Gly).

Preparation (claimed): Preparation of (I) comprises:
(1) (when X2 = NHC(O)) reacting carbonyl compound of formula (VI) and a free amino group of macrolide of formula (VIIa);
(2) (when X2 = OC(O)) reacting a compound of formula (VI) and the free hydroxyl group of a macrolide of formula (VIIb);
(3) (when X1 = -OC(O), Q = NH and X2 = NHC(O)) reacting a macrolide of formula (VIIc) and a free amino group of (VIb);
(4) (when X1 = O(CO)NH and X2 = NHC(O)) reacting a macrolide of formula (VIId) and free amino group compound of formula (VIb);
(5) (when X1 = CH2, Q = NH and X2 = NHC(O)) reacting a macrolide of formula (VIIe) and a compound of formula (VI); or
(6) reacting a macrolide of formula (VIIf), (VIIg) or (VIIh) with a free carboxylic acid of a nonsteroidal antiinflammatory subunit of formula (VIc).

ABEX UPTX: 20040318

SPECIFIC COMPOUNDS - 22 compounds (I) are specifically claimed e.g. Dexamethasone-Gly-Phe-Leu-Gly-Azithromycin of formula (Ia).

The use of 174 compounds is specifically claimed as the drug from which the subunit V is derived e.g. acetyl-salicylic acid; etodolac; flurbiprofen; flunixin; flurbiprofen; S-(+) ibuprofen; indomethacin; ketoprofen; ketorolac; naproxen; suprofen; tolmetin sodium; camptothecin; paclitaxel; methotrexate; doxorubicin; zidovudine; and stavudine.

ADMINISTRATION - Administration of (I) is 0.001-1000 (preferably 3-30) mg/kg/day topically, orally, parenterally, percutaneously, mucosally, buccally, intranasally, intrarectally or intravaginally.

EXAMPLE - Dexamethasone (57 mg) was dissolved in dry dichloromethane (5 ml) in an inert atmosphere and cooled at 0 degrees C. N,N-diisopropylethylamine (0.115 ml) and 1-hydroxybenzotriazole (20.5 mg) were added, followed by the addition of 9-deoxo-9a-aza-9a-(Y-aminopropyl)-9a-

homoerythromycin A (60 mg) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (57.6 mg).
The reaction mixture was stirred in a flow of argon at room temperature for 24 hours and then evaporated under reduced pressure and purified to give Dexamethasone-Gly-Phe-Leu-Gly-Azithromycin (Ia) (14 mg).

DEFINITIONS - Preferred Definitions: In (I);
M = a group of formula (II), with a linkage site through which it is linked to V via linking group L;
either Z, W = CO, CH2, CH-NRtRs, N-R-N, C=N-R-M, or a bond, provided that Z and W are not the same; or
ZW = N(CH3)-CH2, NH-CH2, CH2-NH, C(O)-NH or -NH-C(O);
Rt, Rs = H or alkyl;
R-M = OH, alkoxy, substituted alkoxy or OR-p;
R-N = H, R-p, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, or -C(X)-NRtRs;
X = O or S; group; either
U, Y = H, halo, alkyl, or hydroxyalkyl; or
U = H (preferred); or
Y = CH3;
R1 = OH, -OS2 group (preferred), OR-p, or O;
S1 = a sugar moiety of formula (III) (preferably desosamine sugar);
either R8,R9 = H(preferred); or
R8R9 = a bond; or
R9 = H; and
R8 = -N(CH3)R-y;
Ry = R-p, R-z or -C(O)R-z(preferably CH3, NH2, 1-6C alkylamino or 1-6C dialkylamino);
R-z = alkyl (optionally substituted with 2-7C alkyl, 2-7C alkenyl, 2-7C alkynyl, aryl or heteroaryl), H, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl;
R10 = H or R-p;
S2 = a sugar moiety of formula (IV) (preferably cladinose sugar);
R3 = H or CH3; R11 = H, R-p or O-R11 is a group that with R12 and with C/4 carbon atom forms a CO or epoxy group;
R12 = H or a group that with O-R11 group and with C/4 carbon atom forms a CO or epoxy group;
R2 = H(preferred), OH, OR-P or alkoxy(preferably methoxy);
A = H or CH3 (preferred);
B = CH3 (preferred) or epoxy;
E = H (preferred) or halo; either
R3 = OH, OR-P or alkoxy ; or
R3 = a group that with R5 and with C/11 and C/12 C atoms forms a cyclic carbonate or carbamate;
R4 = 1-4C alkyl (preferably CH3);
R5 = H(preferred), OH(preferred), OR-P, 1-4C alkoxy(preferably methoxy), or a group that with R3 and with C/11 and C/12 C atoms forms a cyclic carbonate or carbamate(preferred);
R6 = H or 1-4C alkyl (preferably OH, methoxy or ethyl);
L = X1-(CH2)m-Q-(CH2)n-X2;
X1 = CH2(preferred), C(O)(preferred), OC(O), NO, OC(O)NH or C(O)NH;
X2 = NH, NHC(O)(preferred), OC(O), C(O), O or CH2;
Q = NH(preferred), CH2 (each group may be optionally substituted by 1-7C alkyl, 2-7C alkenyl, 2-7C alkynyl, C(O)R-X, C(O)OR-X, C(O)NHR-X), or absent(preferred); R-x 1-7C alkyl, aryl or heteroaryl;
m, n = 0-4, provided that if Q is NH, n cannot be 0;
V = an antineoplastic subunit or antiviral subunit (preferably formula (X);
R-a, R-b = H or halo;
R-c = OH, alkoxy, alkyl, thiocarbamoyl, carbamoyl or a valence-bond;

R-d, Re = H, OH, CH3, 1-4C alkoxy, or each are a group that forms a 1,3-dioxolane ring with the other or a valence bond;
R-f = H, OH, Cl, or forming a keto group with the carbon atom it is attached to; and
R-j = H or halo.
Provided that:
(1) the linkage site is at one or more of the following: a) any reactive OH, N, or epoxy group located on S1, S2 or an aglycone oxygen if S1 or/and S2 is cleaved off, b) a reactive N-R-N or -NRtRs or O group located on Z or W, c) a reactive OH group located at any one of R1, R2, R3 and R5, d) any other group that can be first derivatized to a OH or NRtRs group and R-p is hydroxyl or amino protective group;
(2) if W or Z is N-R-N then R3 is a group that forms a cyclic carbamate with W or Z; and
(3) the linkage is through the nitrogen of Z at N/9a position, through the C of R12 or through the oxygen of R11, both at C/4 position of the S2 sugar.

DCSE 860095-0-0-0
SDCN RADE8D

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

L89 ANSWER 12 OF 15 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-122571 [12] WPIX
DOC. NO. CPI: C2004-241622
TITLE: New nonsteroidal compounds useful for the treatment of inflammatory diseases and conditions associated with an undesirable inflammatory **immune** response e.g. excessive secretion of tumor necrosis factor alpha and interleukin-1.
DERWENT CLASS: B05
INVENTOR(S): MARKOVIC, S; MERCEP, M; MESIC, M; TOMASKOVIC, L
PATENT ASSIGNEE(S): (PLIV) PLIVA DD; (PLIV) PLIVA PHARM IND INC; (PLIV) PLIVA DD ZAGREB
COUNTRY COUNT: 104
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2004005309	A2	20040115	(200412)*	EN	78	C07H017-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW						
US 2004097434	A1	20040520	(200434)			A61K031-7048
AU 2003255849	A1	20040123	(200459)			C07H017-00
BR 2003012584	A	20050412	(200526)			C07H017-00
EP 1521763	A2	20050413	(200526)	EN		C07H017-00
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR						
NO 2005000571	A	20050331	(200540)			C07H017-00
JP 2005536488	W	20051202	(200582)		63	C07H017-08
CN 1665829	A	20050907	(200607)			C07H017-00

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004005309	A2	WO 2003-HR35	20030707
US 2004097434	A1 Provisional	US 2002-394671P	20020708
		US 2003-615010	20030707
AU 2003255849	A1	AU 2003-255849	20030707
BR 2003012584	A	BR 2003-12584	20030707
		WO 2003-HR35	20030707
EP 1521763	A2	EP 2003-762824	20030707
		WO 2003-HR35	20030707
NO 2005000571	A	WO 2003-HR35	20030707
		NO 2005-571	20050202
JP 2005536488	W	WO 2003-HR35	20030707
		JP 2004-519020	20030707
CN 1665829	A	CN 2003-816092	20030707

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003255849	A1 Based on	WO 2004005309
BR 2003012584	A Based on	WO 2004005309
EP 1521763	A2 Based on	WO 2004005309
JP 2005536488	W Based on	WO 2004005309

PRIORITY APPLN. INFO: US 2002-394671P 20020708; US 2003-615010 20030707

INT. PATENT CLASSIF.:

MAIN: A61K031-7048; C07H017-00; C07H017-08

SECONDARY: A61K031-7052; A61K031-7084; A61P001-04; A61P009-00; A61P009-10; A61P011-00; A61P011-06; A61P011-08; A61P017-00; A61P017-06; A61P017-16; A61P019-02; A61P019-04; A61P019-06; A61P021-00; A61P027-02; A61P029-00; A61P031-04; A61P037-06

BASIC ABSTRACT:

WO2004005309 A UPAB: 20041019

NOVELTY - Nonsteroidal compounds (I) and their salts, solvates and individual diastereoisomers are new.

DETAILED DESCRIPTION - Nonsteroidal compounds of formula M-L-D (I) and their salts, solvates and diastereoisomers are new.

M = macrolide subunit;

D = nonsteroidal subunit; and

L = linker molecule to which each of M and D are covalently linked.

An INDEPENDENT CLAIM is also included for the preparation of (I).

ACTIVITY - Antiinflammatory; Antiasthmatic; Antiallergic; Antiarthritic; Antirheumatic; Antiulcer; Antipsoriatic; Antigout; Antibacterial; Respiratory-Gen.; Gastrointestinal-Gen.; Dermatological; Cardiant; CNS-Gen.; Osteopathic; Litholytic; Ophthalmological; **Immunosuppressive**; Cytostatic.

MECHANISM OF ACTION - Tumor necrosis factor- alpha antagonist; interleukin-1 antagonist.

(I) were tested for their lipopolysaccharide (LPS)-induced excessive secretion of TNF- alpha in vivo in mice as in Badger A. M. et al., J. of Pharmac. and Env. Therap. 279 1996 1453-1461. The result showed that the percentage inhibition of the macrolide compound of formula (Ia) was 70%.

USE - (I) is useful for the manufacture of a medicament for the treatment of inflammatory diseases, disorders and conditions characterized by or associated with undesirable inflammatory **immune** response,

especially diseases and conditions induced by or associated with excessive secretion of tumor necrosis factor (TNF)- alpha and interleukin (IL-1). (I) is also useful for treatment of inflammatory conditions and **immune** or anaphylactic disorders of the lungs, joints, eyes, bowel, skin and heart (particularly asthma, adult respiratory distress syndrome, bronchitis, cystic fibrosis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, uveitis, conjunctivitis, inflammatory bowel conditions, Crohn's disease, ulcerative colitis, distal proctitis, psoriasis, eczema, dermatitis, **coronary infarct** damage, chronic inflammation, endotoxin shock and smooth muscle proliferation disorders) and conditions associated with infiltration of leukocytes into inflamed tissue (all claimed).

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B04-C01C; B06-H; B07-H; B14-C02; B14-C03; B14-C06; B14-C09; B14-E08; B14-E10; B14-F01B; B14-G02D; B14-H01B; B14-J05; B14-K01; B14-K01A; B14-L06; B14-L07; B14-N01; B14-N03; B14-N07; B14-N17; B14-S06

TECH UPTX: 20041019

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (Claimed): Preparation of (I) comprises:

(a) (when X2 = NHC(O)) reaction of a carbonyl compound of formula L1C(O)D (V) with a free amino group of a macrolide of formula MX1(CH2)mQ(CH2)nNH2 (VIa);

(b) (when X2 = OC(O)) reaction of (V) with the free hydroxyl group of a macrolide of formula MX1(CH2)mQ(CH2)nOH (VIb);

(c) (when X1 = OC(O), Q = NH and X2 = NHC(O)) reaction of a macrolide substituted at the 6 or 4'' position by an acryloyloxy group and a free amino group of formula H2NKNHC(O)D (VId);

(d) (when X1 = OC(O)NH and X2 = NHC(O)) reaction of a macrolide of partial formula (VIe) and (VId);

(e) reaction of a macrolide of partial formula (VIg) with (V); or

(f) reaction of a macrolide substituted by a group OC(O)KL2 or KL2 or of partial formula (VIIh) with a free carboxylic acid of nonsteroidal anti-inflammatory subunit.

L1, L2 = leaving group.

ABEX UPTX: 20041019

SPECIFIC COMPOUNDS - 23 Compounds (I) are specifically claimed e.g. an indomethacin linked macrolide compound of formula (Ia).

ADMINISTRATION - Administration is 0.001-1000 (preferably 3-30) mg/kg/day, topically, orally, parenterally, percutaneously, mucosally, buccally, intranasally, intrarectally or intravaginally.

EXAMPLE - To a solution of indomethacin (104 mg) in dry dichloromethane (5 ml) under argon, triethylamine (0.38 ml), 1-hydroxybenzotriazole (80 mg), ML2 of formula (IIA) (230 mg) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (235 mg) were added. The reaction mixture was stirred for 24 hours at room temperature in a flow of argon, then evaporated to a smaller volume under reduced pressure and purified on a silica gel column to give the macrolide compound ML2-indomethacin amide (Ia, 127 mg).

DEFINITIONS - Preferred Definitions:

M = a group of formula (II) with a linkage site through which it is linked to D via linking group L;

Z1, W1 = C(O), CH2, CHNRtRs, N(RN), C=N(RM) or a bond but may not both be the same;

Rt, Rs = H or alkyl;

RM = OH, alkoxy, substituted alkoxy or OR-p;

RN = H, Rp, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, or C(X)NRtRs;
X = O or S;
U1 = H, halo, alkyl, or hydroxyalkyl;
Y1 = H, halo, alkyl, or hydroxyalkyl;
R1 = OH, ORp, OS2 group or O;
S1 = sugar moiety of formula (III) (preferably desosamine); either
R8, R9 = H; or
R8 = N(CH3)Ry and R9 = H; or
R8+R9 = bond;
Ry = Rp, Rz or C(O)Rz;
Rz = H, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or alkyl (optionally substituted by 2-7C alkyl, 2-7C alkenyl, 2-7C alkynyl, aryl or heteroaryl);
R10 = H or Rp;
S2 = sugar moiety of formula (IV) (preferably cladinose sugar);
R3' = H or methyl;
R11 = H or Rp;
R12 = H; or
OR11+R12 = C(O) or epoxy;
R2 = H, OH, ORp or alkoxy;
A = CH3 or H;
B1 = methyl or epoxy;
E = H or halo;
R3 = OH, ORp or alkoxy or R3 is a group that with R5 and with C/11 and C/12 C forms a cyclic carbonate or carbamate, or if W or Z is N-R-N R3 is a group that with W or Z forms a cyclic carbamate (preferably OH or a group that with R3 is a group that with R5 and with C/11 and C/12 C forms a cyclic carbonate or carbamate bridge);
R4 = 1-4C alkyl;
R5 = H, OH, ORp or 1-4C alkoxy; or
R3+R5 = cyclic carbonate or carbamate; or
if W1 or Z1 = N(RN) then R3 forms a cyclic carbamate with W1 or Z1;
R6 = H or 1-4C alkyl;
Rp = OH or amino protecting group;
L = X1(CH2)mQ(CH2)nX2;
D = group derived from nonsteroidal antiinflammatory drugs such as aceclofenac, acemetacin, acetaminophen, acetaminosalol, acetylsalicylic acid, acetylsalicylic-2-amino-4-picoline-acid, 5-aminoacetylsalicylic acid, alclofenac, aminoprofen, amfenac, ampyrone, ampiroxicam, anileridine, bendazac, benoxaprofen, bermoprofen, alpha-bisabolol, bromfenac, 5-bromosalicylic acid acetate, bromosaligenin, bucloxic acid, butibufen, carprofen, celexocib, cromoglycate, cinmetacin, clindanac, clopirac, sodium diclofenac, diflunisal, ditazol, droxicam, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenac, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glutametacin, glycol salicylate, ibufenac, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, montelukast, nabumetone, naproxen, niflumic acid, nimesulide, olsalazine, oxaceprol, oxaprozin, oxyphenbutazone, paracetamol, parsalmide, perisoxal, phenylacetyl-salicylate, phenylbutazone, phenylsalicylate, pyrazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, reserveratol, salacetamide, salicylamide, salicylamide-O-acetyl acid, salicylsulfuric acid, salicin, salicylamide, salsalate, sulindac, suprofen, suxibutazone, tamoxifen, tenoxicam, tiaprofenic acid, tiaramide, ticlopridine, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepirac, tomoxiprol, zafirlukast or cyclosporin;
X1 = CH2, OC(O), C(O), N-O (sic), OC(O)NH or C(O)NH;
X2 = NHC(O), NH, OC(O), C(O), O or CH2;

Q = NH or CH2 (both optionally substituted by 1-7C alkyl, 2-7C alkenyl, 2-7C alkynyl, C(O)Rx, C(O)ORx or C(O)NHRx) or absent;
Rx = 1-7C alkyl, aryl or heteroaryl;
m, n = 0-4, provided that when Q = NH then n is not 0;
Provided that the linkage site is at one or more of:
(a) any reactive OH, N, or epoxy group located on S1, S2, or an aglycone oxygen if S1 or/and S2 is cleaved off;
(b) a reactive N(RN) or NRtRs or O group located on Z1 or W1;
(c) a reactive hydroxy group located at any one of R1-R3 and R5; or
(d) any other group that can be first derivatized to a hydroxy or NRtRs group.
DCSE 841364-1-0-0
SDCN RAD07D

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

L89 ANSWER 13 OF 15 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-234905 [24] WPIX
DOC. NO. CPI: C2001-070327
TITLE: New compounds including drug groups used for treating oxidative stress and/or endothelial disorders of moderate intensity.
DERWENT CLASS: B05
INVENTOR(S): DEL SOLDATO, P; DEL SOLDATA, P
PATENT ASSIGNEE(S): (NICO-N) NICOX SA
COUNTRY COUNT: 84
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2001012584	A2	20010222	(200124)*	EN	93	C07C219-14
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW						
W: AE AL AU BA BB BG BR CA CN CR CU CZ DM EE GD GE HR HU ID IL IN IS JP KP KR LC LK LR LT LV MA MG MK MN MX NO NZ PL RO SG SI SK TR TT UA US UZ VN YU ZA						
AU 2000065670	A	20010313	(200134)			C07C219-14
BR 2000013264	A	20020416	(200234)			C07C219-14
NO 2002000623	A	20020409	(200238)			C07C000-00
KR 2002032552	A	20020503	(200270)			C07D499-68
EP 1252133	A2	20021030	(200279)	EN		C07C219-14
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI						
IT 1314184	B	20021206	(200317)			A61K031-00
JP 2003515526	W	20030507	(200331)		116	C07C203-04
HU 2002003939	A2	20030328	(200333)			C07C219-14
ZA 2002000628	A	20030625	(200348)		110	C07C000-00
CN 1433396	A	20030730	(200365)			C07C219-14
MX 2002001519	A1	20030701	(200366)			A61K031-21
NZ 516889	A	20041029	(200474)			C07C219-14
EP 1252133	B1	20050608	(200543)	EN		C07C219-14
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU MC NL PT RO SE SI						
AU 781643	B2	20050602	(200544)			C07C219-14
IN 2002000187	P4	20050304	(200547)	EN		C07C219-14
DE 60020741	E	20050714	(200549)			C07C219-14
EP 1593664	A1	20051109	(200573)	EN		C07C069-708
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RU 2264383	C2	20051120 (200576)	C07C219-14
DE 60020741	T2	20051215 (200582)	C07C219-14
NZ 535559	A	20051223 (200612)	C07D333-00

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001012584	A2	WO 2000-EP7225	20000727
AU 2000065670	A	AU 2000-65670	20000727
BR 2000013264	A	BR 2000-13264	20000727
		WO 2000-EP7225	20000727
NO 2002000623	A	WO 2000-EP7225	20000727
		NO 2002-623	20020208
KR 2002032552	A	KR 2002-701883	20020209
EP 1252133	A2	EP 2000-953102	20000727
		WO 2000-EP7225	20000727
IT 1314184	B	IT 1999-MI1817	19990812
JP 2003515526	W	WO 2000-EP7225	20000727
		JP 2001-516885	20000727
HU 2002003939	A2	WO 2000-EP7225	20000727
		HU 2002-3939	20000727
ZA 2002000628	A	ZA 2002-628	20020123
CN 1433396	A	CN 2000-814049	20000727
MX 2002001519	A1	WO 2000-EP7225	20000727
		MX 2002-1519	20020211
NZ 516889	A	NZ 2000-516889	20000727
		WO 2000-EP7225	20000727
EP 1252133	B1	EP 2000-953102	20000727
		WO 2000-EP7225	20000727
AU 781643	B2	AU 2000-65670	20000727
IN 2002000187	P4	IN 2002-CN187	20020204
		WO 2000-EP7225	
DE 60020741	E	DE 2000-00020741	20000727
		EP 2000-953102	20000727
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EP 1593664	A1 Div ex	EP 2000-953102	20000727
		EP 2005-104064	20000727
RU 2264383	C2	WO 2000-EP7225	20000727
		RU 2002-103509	20000727
DE 60020741	T2	DE 2000-00020741	20000727
		EP 2000-953102	20000727
		WO 2000-EP7225	20000727
NZ 535559	A Div ex	NZ 2000-270700	20000727
		NZ 2000-535559	20000727

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000065670	A Based on	WO 2001012584
BR 2000013264	A Based on	WO 2001012584
EP 1252133	A2 Based on	WO 2001012584
JP 2003515526	W Based on	WO 2001012584
HU 2002003939	A2 Based on	WO 2001012584
MX 2002001519	A1 Based on	WO 2001012584
NZ 516889	A Div in	NZ 535559
	Based on	WO 2001012584
EP 1252133	B1 Based on	WO 2001012584
AU 781643	B2 Previous Publ.	AU 2000065670

		Based on	WO 2001012584
DE 60020741	E	Based on	EP 1252133
		Based on	WO 2001012584
EP 1593664	A1	Div ex	EP 1252133
RU 2264383	C2	Based on	WO 2001012584
DE 60020741	T2	Based on	EP 1252133
		Based on	WO 2001012584
NZ 535559	A	Div ex	NZ 516889

PRIORITY APPLN. INFO: IT 1999-MI1817 19990812
INT. PATENT CLASSIF.:
MAIN: A61K031-00; A61K031-21; C07C000-00; C07C069-708; C07C203-04; C07C219-14; C07D333-00; C07D499-68
SECONDARY: A61K031-221; A61K031-222; A61K031-235; A61K031-365; A61K031-366; A61K031-43; A61K031-4365; A61K031-437; A61K031-454; A61K031-473; A61K031-496; A61K031-663; A61K031-704; A61K038-00; A61P001-02; A61P003-06; A61P003-10; A61P007-02; A61P009-08; A61P009-12; A61P011-06; A61P011-08; A61P011-10; A61P011-12; A61P019-08; A61P025-02; A61P025-28; A61P029-00; A61P031-04; A61P031-12; A61P035-00; A61P037-08; A61P043-00; C07C069-618; C07C219-10; C07C219-22; C07C219-24; C07C219-30; C07C229-42; C07C233-25; C07D213-00; C07D219-10; C07D295-08; C07D307-80; C07D309-30; C07D401-12; C07D471-04; C07D495-00; C07D495-04; C07D499-48; C07F009-38; C07H015-252

BASIC ABSTRACT:

WO 200112584 A UPAB: 20051130

NOVELTY - New compounds (I) including drug groups are new.

DETAILED DESCRIPTION - Compounds of formula A-B-N(O)s (I) are new.

s = 1 or 2, preferably 2;

A = R-T1;

R = a drug group;

T1 = (CO)t or (X)t;

X = O, S or NR1c;

t, t' = 0 or 1;

provided that when t = 1 when t' = 0 and t = 0 when t' = 1;

B = TB-X2-O;

TB = CO when t = 0 or X when t' = 0;

X2 = a bivalent group such that the corresponding precursor TB-X2-OH of B does not meet test 5 and meets test 4A and TB = CO and t = 0, with the free valence of TB saturated with OZ or ZI-N(ZII) or TB = X and t' = 0 and the free valence of TB is saturated with H;

Z = H or R1a;

R1a = 1-10 (preferably 1-5)C alkyl and

ZI, ZII = a group Z;

provided that the drug A = R-T1, where the free valence is saturated when t' = 0, with OZ or ZI-N(ZII) and when t = 0 with X-Z meets at least one of tests 1-3.

Test 1 (NEM) is a test carried out in vivo on 4 groups of rats (each group containing 10 rats), the controls (2 groups) and the treated (2 groups) of which one group of the controls and one group of the treated respectively are administered with one dose of 25 mg/kg subcutaneously N-ethylmaleimide (NEM). The controls are treated with the carrier and the treated groups with carrier and drug A = R-T1 with saturated free valence. The drug is administered at a dose equivalent to the maximum dose tolerated by the rats that did not receive NEM. The drug can be used to prepare (I) when the group treated with NEM, carrier and drug shows gastrointestinal damage or in the group treated with NEM, carrier and drug are observed gastrointestinal damage greater than that of the group

treated with carrier or of the group treated with the carrier and NEM.

Test 2 (CIP) is an in vitro test where human endothelial cells from the umbilical vein are harvested under standard conditions, then divided into 2 groups (each replicated 5 times), of which one is treated with a mixture of the drug 10-4 concentration in culture medium and the other group with carrier. Then cumene hydroperoxide (CIP) having 5 mM concentration in the culture medium is added to each group. The drug can be use to prepare (I) when a statistically significant inhibition of the apoptosis induced by CIP is not obtained with p less than 0.01 with respect to the group treated with carrier and CIP.

Test 3 (l-NAME) is an in vivo test carried out on 4 groups of rats (each containing 10 rats) for 4 weeks and receiving drinking water, the controls (2 groups) and the treated (2 groups), of which 1 group of controls and of treated respectively receive in the above weeks water containing N- omega -nitro-L-arginine methyl ester (L-NAME) at a concentration of 400 mg/l. Controls in the 4 weeks are administered with carrier and the treated in the 4 weeks with carrier and drug, each once a day. The drug is administered at the maximum dose tolerated by the group of rats not pretreated with L-NAME. After 4 weeks, water supply is stopped for 24 hours and then the rats are sacrificed. Blood pressure is determined 1 hour before sacrifice. After sacrifice, the plasma glutamic pyruvic transaminase (GPT) is determined and the gastric tissue is examined. The drug can be used to prepare (I) when in group treated with L-NAME, carrier and drug, greater hepatic damage and/or **cardiovascular** damage are found in comparison respectively with the group treated with the carrier or carrier and drug or carrier and L-NAME.

Test 4A met by the compound precursor B is an in vitro test in which part of an erythrocyte suspension kept at 4 deg. C for 4 days and isolated from Wistar male rats and suspended in physiological solution buffered at pH 7.4 with phosphate buffer, is centrifuged at 1000 rpm for 5 minutes. 0.1 ml Centrifuged erythrocytes are diluted with sodium phosphate buffer pH 7.4 at 50 ml. Aliquots of 3.5 ml are taken and incubated at 37degC in the presence of cumene hydroperoxide at a concentration of 270 mu M and the suspension turbidity determined at 710 nm at intervals of 30 minutes to establish the time (Tmax) at which occurs the maximum turbidity that corresponds to the maximum amounts of cells lysed by cumene hydroperoxide (haemolysis assumed to be 100%). Alcoholic solutions of the compounds precursors of B are added to 3.5 ml aliquots of the dilutes suspension of centrifuged erythrocytes to give a final concentration of 2 mm of the precursor of B. Resulting suspension is preincubated for 30 minutes. Cumene hydroperoxide is added to give the same above indicated final concentration and at Tmax is determined the percentage of haemolysis inhibition in the sample from the ratio, multiplied by 100, between absorbance of sample containing erythrocytes, precursor of B and cumene hydroperoxide respectively and that of sample containing erythrocytes and cumene hydroperoxide. Precursors of B meet the test if they inhibit haemolysis induced by cumene hydroperoxide by more than 15%.

Test 5 is an analytical determination carried out by adding aliquots of 10-4 M methanol solutions of precursor B or B1 or of C = Tc-Y-H, having the free valence saturated, to solution formed by admixing 2 mM solution of deoxyribose in water with 100 mM phosphate buffer and 1 mu M FeII(NH4)2(SO4)2. After thermostating at 37 deg. C for 1 hour, aliquots of aqueous solutions of trichloroacetic acid (2.8%) and of thiobarbituric acid (0.5M) are added and heating is effected at 100 deg. C for 15 minutes. Absorbance of tested solutions is read at 532 nm. Inhibition induced by precursor B or B1 or C = Tc-Y-H in the confront of radical production by FeII is calculated as a percentage by using (1-As/Ac) x 100.

As and Ac are respectively absorbance values of solution containing tested compound and iron salt and that of solution containing iron salt.

Test 5 is met when inhibition percentage is at least 50%.

In (I), when X2 of B is 1-20C alkylene or 5-7C cycloalkylene (optionally substituted), the drugs of formula A = R-T1 with free valence saturated, do not belong to drugs used in incontinence, antithrombotic drugs (ACE inhibitors), prostaglandins and anti-inflammatory drugs (NSAIDs and corticosteroids), but not excluding paracetamol and sulindac.

N.B. The definitions given in the specification are not clear.

ACTIVITY - Antioxidant; cardiant; vasotropic; hypotensive; cerebroprotective; antiarteriosclerotic; antiarthritic; anti-inflammatory; neuroprotective; dermatological; antibacterial.

MECHANISM OF ACTION - None given.

USE - Used for treating oxidative stress and/or endothelial dysfunctions of moderate intensity, which cause myocardial and **vascular ischemia**, hypertension, **stroke**, arteriosclerosis, rheumatoid arthritis and connected inflammatory diseases, asthma and connected inflammatory diseases, ulcerative and non ulcerative dyspepsias, intestinal inflammatory diseases, **Alzheimer**'s disease, impotence, incontinence, eczema, neurodermatitis, acne and infectious diseases.

ADVANTAGE - (I) Have higher efficacy and lower toxicity.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B02-T; B05-B01G; B06-A01; B06-D05; B06-D08; B06-D13; B06-F03; B07-A02B; B07-A04; B07-B01; B07-B03; B07-D01; B07-D02; B07-D05; B07-E01; B07-F01; B10-A05; B10-B03B; B10-E04C; B14-A01; B14-C03; B14-C09; B14-F01; B14-F02; B14-F02B; B14-F07; B14-J01; B14-N17; B14-S08

TECH UPTX: 20010502

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises e.g. reacting a sodium carboxylate compound of formula (II) with a halogen compound of formula (III) and converting the obtained compound of formula (IV) to a compound of formula (I').

R3 = OH or Hal.

Preferred compounds: The precursor compounds of B are 1,4-butandiol, 6-hydroxyhexanoic acid, 4-hydroxybutyric acid, N-ethyldiethanolamine, diethylene glycol, thiodiethylene glycol, 1,4-dioxane-2,6-dimethanol, tetrahydropyrane-2,6-dimethanol, 4H-pyrane-2,6-dimethanol, tetrahydrothiopyrane-2,6-dimethanol, 1,4-dithiane-2,6-dimethanol, cyclohexene-1,5-dimethanol, thiazole-2,5-dimethanol, thiophene-2,5-dimethanol or oxazole-2,5-dimethanol, preferably N-methyldiethanolamine, diethylene glycol or thiodiethylene glycol.

The precursor drugs of (I) comprises anti-inflammatory, analgesic drugs, bronchodilators and drugs active on the cholinergic system, expectorant mucolytics, antiasthmatic antiallergic drugs, antihistaminic drugs, ACE inhibitors, beta blockers, antithrombotic drugs, vasodilators, antidiabetics, antitumoral, antiulcer drugs, antihyperlipidemic drugs, antibiotics, antiviral drugs, bone resorption inhibitors or antidementia drugs.

ABEX UPTX: 20010502

EXAMPLE - Silver nitrate (4.56 g) was added to a solution of 4-bromobutyric acid 4'-acetyl amino phenyl ester (5.33 g) in acetonitrile (80 ml) and the mixture was heated for 16 hours away from light at 80degreesC, then cooled to room temperature. The mixture was then filtered to remove the silver salts and evaporated under reduced pressure. The residue was purged by chromatography on silica gel eluting with n-hexane/ethyl acetate 4/6 to give 4-nitroxybutyric acid 4'-acetylaminophenyl ester (4.1 g), m. pt. 80-83degreesC.

DCSE 377182-0-0-0

CN.P NITROSULINDAC
CN.S [6-Fluoro-3-(4-methanesulfinyl-benzylidene)-2-methyl-3H-inden-1-yl]-acetic acid 4-nitrooxy-butyl ester
SDCN RA300J

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

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ACCESSION NUMBER: 2002-024722 [03] WPIX
CROSS REFERENCE: 2000-450767 [35]
DOC. NO. CPI: C2002-006829
TITLE: Treating precancerous lesions and neoplasms by administering indenyl hydroxamic acid, (hydroxy)urea or urethane derivatives.
DERWENT CLASS: B05
INVENTOR(S): BRENDEL, K; GROSS, P; PAMUKCU, R; PIAZZA, G A; SPERL, G
PATENT ASSIGNEE(S): (CELL-N) CELL PATHWAYS INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 6300346	B1	20011009 (200203)*			20	A61K031-44

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 6300346	B1 Div ex	US 1997-823863	19970325
		US 2000-520667	20000307

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 6300346	B1 Div ex	US 6071934

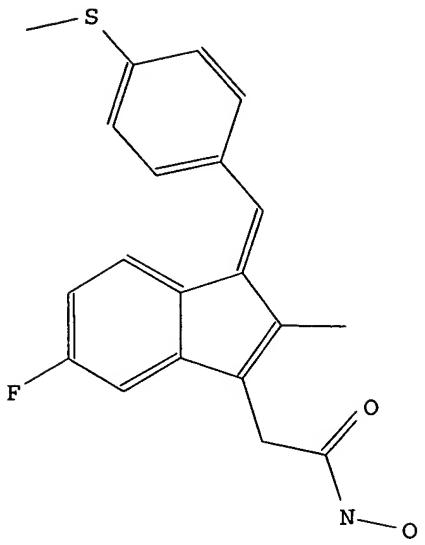
PRIORITY APPLN. INFO: US 1997-823863 19970325; US 2000-520667 20000307
INT. PATENT CLASSIF.:
MAIN: A61K031-44
SECONDARY: A61K031-17; A61K031-38
BASIC ABSTRACT:
US 6300346 B UPAB: 20020114
NOVELTY - Treating precancerous lesions and neoplasms comprises administering indenyl hydroxamic acid, (hydroxy)urea or urethane derivatives (I).
DETAILED DESCRIPTION - Treating precancerous lesions and neoplasms comprises administering indenyl hydroxamic acid, (hydroxy) urea or urethane derivatives of formula (I).
R1, R5 = H or lower alkyl;
R2, R3 = H, lower alkyl, phenyl or heteroaryl (both optionally substituted by lower alkyl or R7), lower alkyl monosubstituted by optionally substituted phenyl or heteroaryl;
R7 = -OR8, -SR9, -S(O)nR9, -CN, -CO2R8 or halo;
R8 = H or R9;
R9 = lower alkyl;

R4 = H, lower alkyl, lower alkynyl, lower alkenyl, -OR8, -C(O)R8, -NO2, N(R8)2, -NR8C(O)R8, -R10N(R8)2, SO2N(R8)2-SR9, -R10OH, -S(O)nR9, -CN, -CO2R8, -CON(R8)2, halo, cycloalkyl, -R10 or cycloalkoxy;
R10 = lower alkyl;
R6 = H or -OM;
M = H, cation or -C(O)R11;
R11 = lower alkyl or phenyl optionally substituted by lower alkyl or R7;
m = 0-4;
n = 1 or 2;
p = 0-2;
Z = lower alkyl, NR12R13 or OR13;
R12 = -OM or R13;
R13 = H, lower alkyl, lower alkynyl, lower alkenyl, lower (substituted) alkyl-(substituted) aryl, amino, alkylamino, cycloalkyl, aryl, heteroaryl, adamantyl or substituted polyaminalkyl, or
R12 + R13 = 3-6C heterocyclic ring containing 1 or 2 heteroatoms selected from N, S or O,
provided that R12 is -OM, when R6 is H or n is 0.
ACTIVITY - Cytostatic.
In an assay using human colon carcinoma cell line HT-29, (Z)-N-(5-fluoro-2-methyl-1-(para-methylsulfonyl-benzylidene)-inden-3-yl)-methyl)-N'-benzylurea (Ia) exhibited an IC50 value of 1.6-3.2 mu M for inhibition of tumor cells.
MECHANISM OF ACTION - None given in source material.
USE - Used for treating precancerous lesions and neoplasms (claimed), including breast cancer, lesions of the skin e.g. malignant melanoma and basal cell carcinoma, colonic adenomatous polyps e.g. colon cancer and for treating apoptosis, for treating precancerous lesions of the cervix e.g. cervical dysplasia and for treating prostatic dysplasia.
ADVANTAGE - (I) Reduces illness and death from cancer and prevents side effects such as hair loss, weight loss, vomiting and bone marrow **immune** suppression.
Dwg.0/0

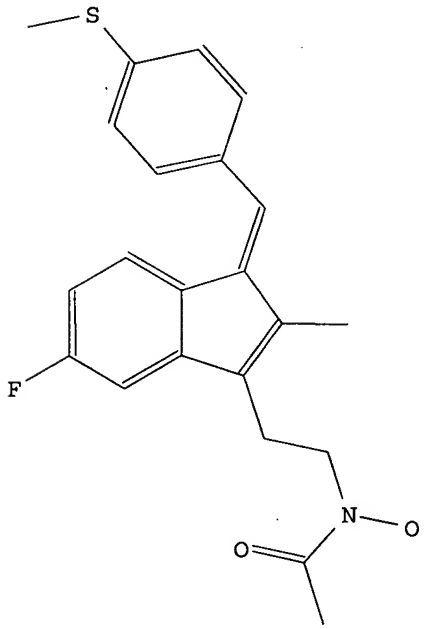
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B07-H; B10-A08; B10-A10; B10-A13B; B10-A16; B10-A19; B10-A22; B10-D03; B14-H01
ABEX UPTX: 20020114
ADMINISTRATION - Administration is oral or rectal.

DEFINITIONS - Preferred definitions:
R4 = fluoro;
R3, R5 = H;
R2 = methylsulfonyl phenyl;
p = 1, and
m = 1.

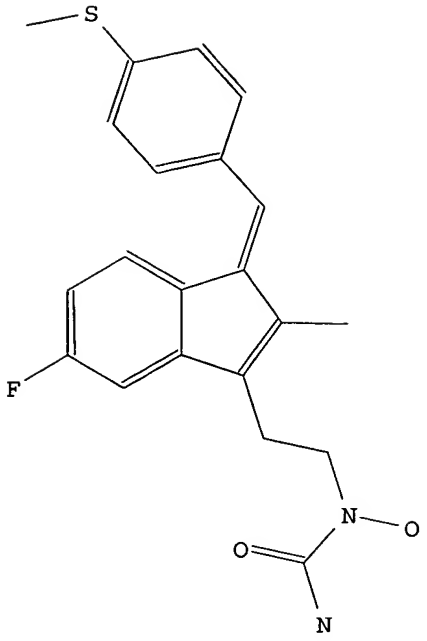
DCSE 481550-0-0-0
CN.S 2-[6-Fluoro-2-methyl-3-(4-methylsulfanyl-benzylidene)-3H-inden-1-yl]-N-hydroxy-acetamide
SDCN RA5TO4



DCSE 481551-0-0-0
CN.S N-{2-[6-Fluoro-2-methyl-3-(4-methylsulfanyl-benzylidene)-3H-inden-1-yl]-ethyl}-N-hydroxy-acetamide
SDCN RA5TO5



DCSE 481552-0-0-0
SDCN RA5TO6



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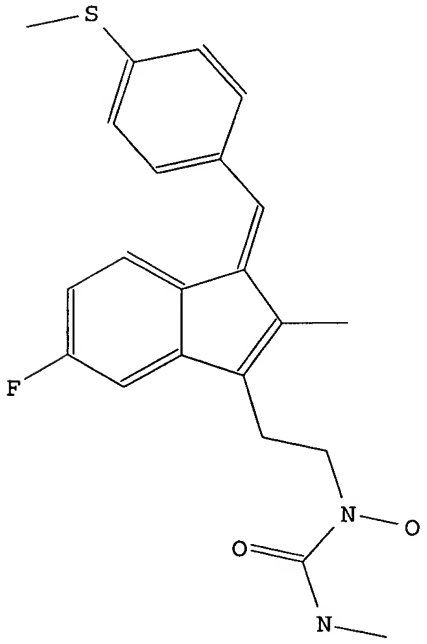
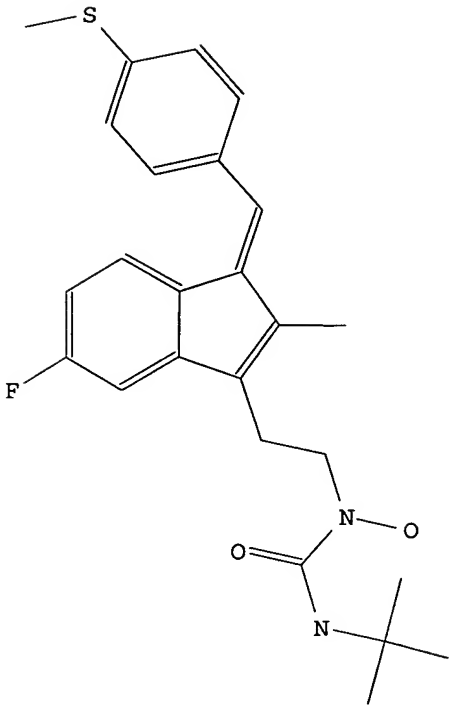
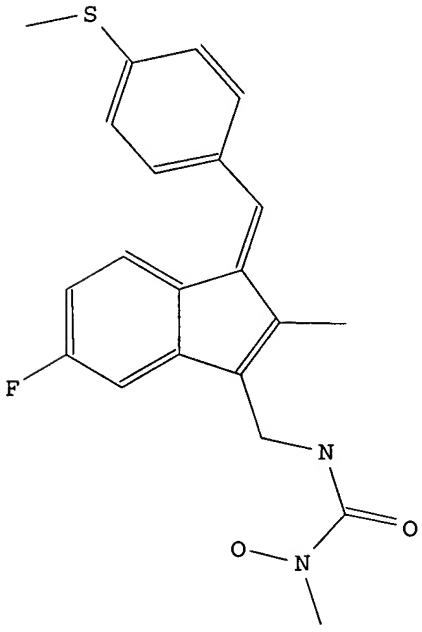
SDCN RA5TO7



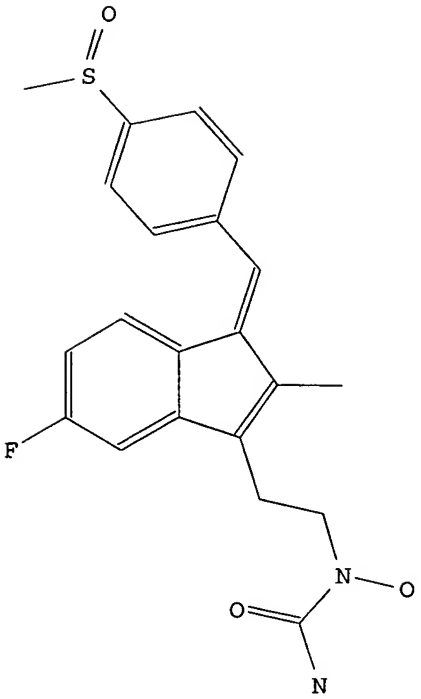
DCSE 481554-0-0-0
SDCN RA5TO8



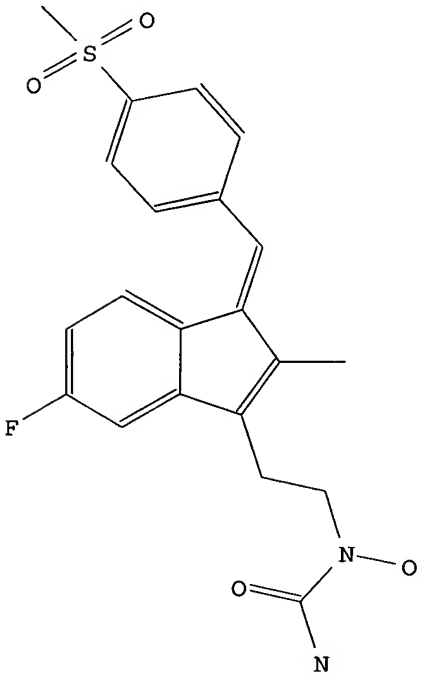
DCSE 481556-0-0-0
SDCN RA5TOA



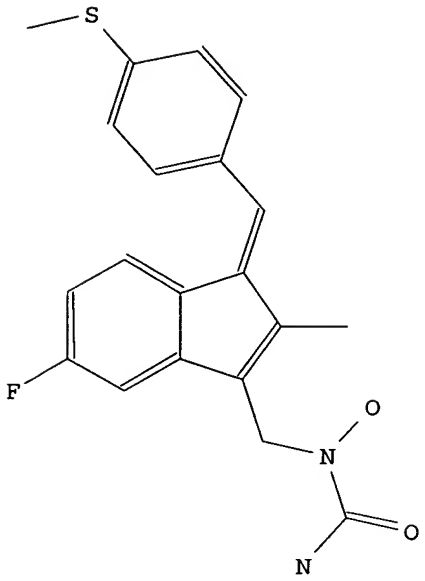
DCSE 481559-0-0-0
SDCN RA5TOD



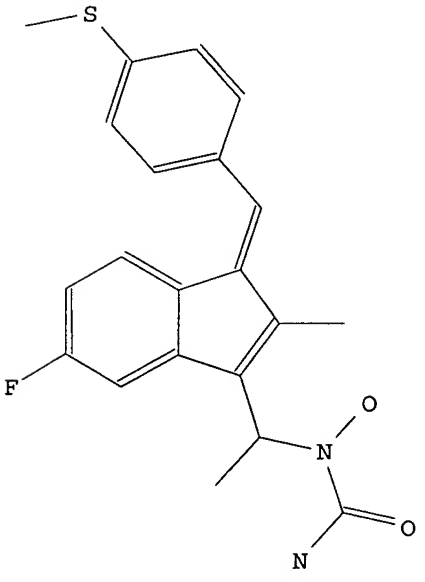
DCSE 481561-0-0-0
SDCN RA5TOF



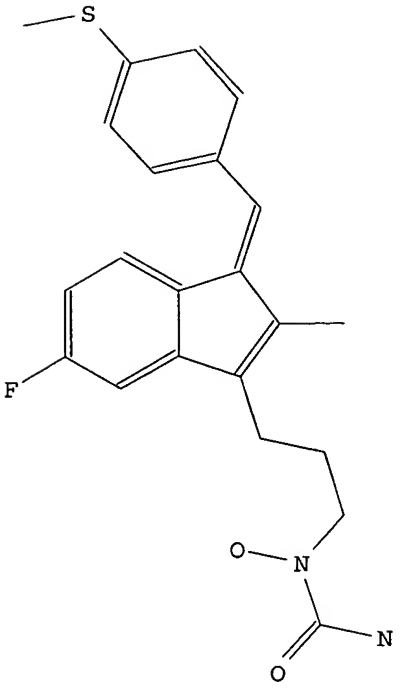
DCSE 481563-0-0-0
SDCN RA5TOH



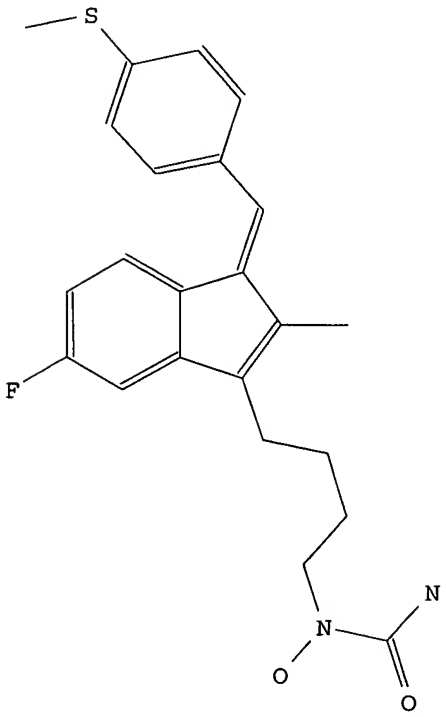
DCSE 481564-0-0-0
SDCN RA5TOI



DCSE 481565-0-0-0
SDCN RA5TOJ



DCSE 481566-0-0-0
SDCN RA5TOK



L89 ANSWER 15 OF 15 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 1999-600539 [51] WPIX
CROSS REFERENCE: 1995-358324 [46]
DOC. NO. CPI: C1999-174810
TITLE: Treatment of precancerous lesions, inhibition of growth of neoplastic cell, and regulation of apoptosis in cells.
DERWENT CLASS: B03 B05
INVENTOR(S): BRENDEL, K; GROSS, P; PAMUKCU, R; PIAZZA, G A; SPERL, G
PATENT ASSIGNEE(S): (CELL-N) CELL PATHWAYS INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 5965619	A	19991012	(199951)*		20	A01N037-10

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 5965619	A	Cont of	US 1996-662458	19960613
			US 1997-996944	19971223

PRIORITY APPLN. INFO: US 1996-662458 19960613; US 1997-996944 19971223
INT. PATENT CLASSIF.:
MAIN: A01N037-10
SECONDARY: A01N037-34; A01N043-54
BASIC ABSTRACT:
US 5965619 A UPAB: 19991207
NOVELTY - Treatment of precancerous lesions, inhibition of growth of neoplastic cell, and regulation of apoptosis in cells comprises administration of an indene derivative (I).
DETAILED DESCRIPTION - Treatment of precancerous lesions, inhibition of growth of neoplastic cell, and regulation of apoptosis in cells comprises administration of an indene derivative of formula (I).
R = H, lower alkyl, trihaloalkyl or cycloalkyl;
R1 = CHR4COOR, CH=CHR, (CH2)mCONRR4, CHOHCHOHR, or (CH2)mR5;
R4 = H, OH, lower alkyl, amino, alkylamino or benzylamino;
R5 = R, OR, SR, S-phenyl, S-phenyl-(R8)m, SOR, SO2R, CN, OCOR, NHCOR, NRCOOR, NRCONRR4, OCONRR4, NRR4, halo, or Y;
Y = pyrimidinyl, pyridyl, imidazolyl, tetrazolyl, isothiazolyl or morpholinyl;
m = 1-4;
R2 = NHSO2R6, H, lower alkyl, NHCOR6, NRR4, OR7, trihaloalkyl, SO2NRR4, SO2NHY, SO2NHX, SO2CF3, CN, SO2NR4COR6, or COOR6; or
R2+R2 = O(CH2)m'O;
R7 = H, R, lower alkenyl, or lower alkynyl;
X = CONH2, CSNH2 or C(=NH)NH2;
R3 = H, OH, lower alkyl, lower alkoxy, OR7, halo, OCH2-phenyl (optionally substituted by R8), CH2OR6, SR6, SCH2-phenyl (optionally substituted by R8), CH2SR6, SOR6, SO2R6, OCOR6, NRR4, NH2, NR4COOR6, NHCOR6, or OCOOR6; or
R3+R3 = O(CH2)m'O;
m' = 1-3;
R6 = R, CF3 or phenyl (optionally substituted by R8);
R8 = H, lower alkyl, lower alkoxy, NH2, lower alkylamino, lower dialkylamino, halo, CN, or lower haloalkyl; and
n, p = 1-3.
ACTIVITY - Cytostatic; antineoplastic; neuroprotective; nootropic;

antiparkinsonian; **immunosuppressant**; antirheumatic; antiarthritic; antiviral; antibacterial; anti-HIV.

(I) were tested for their ability to inhibit the incidence of mammary lesions in organ culture systems. Female BALB/c mice, 28 days old, were treated for 9 days with a combination of estradiol (1 micro g) and progesterone (1 mg) daily in order to prime the glands to be responsive in vitro. The animals were sacrificed and thoracic mammary glands were excised and incubated for 10 days in growth media supplemented with growth-promoting hormones. Lesions were induced in the mammary glands. (Z)-5-Fluoro-2-methyl-1-(4-chlorobenzylidene)-3-indenylacetic acid (Ia) dissolved in dimethyl sulfoxide was added to the culture media for the duration of the culture period. At 10 micro M (Ia) showed 50 % inhibition of the mammary lesions, and at 100 micro M (Ia) showed 100 % inhibition.

MECHANISM OF ACTION - Cyclooxygenase (COX) inhibitor.

USE - The method is used for the treatment of precancerous lesions, inhibition of growth of neoplastic cell, and regulation of apoptosis in cells (claimed). The method can be used in the treatment of diseases such as benign prostatic hyperplasia, **neurodegenerative** diseases (e.g. **Parkinson**'s disease), **autoimmune** diseases (e.g. multiple sclerosis and rheumatoid arthritis), infectious diseases (e.g. acquired **immune** deficiency syndrome (AIDS)), adenomatous growths in colonic, breast or lung tissues, dysplasic nevus syndrome, polyposis syndromes, colonic polyps, cervical dysplasia, bronchial dysplasia, actinic keratosis, malignant melanomas, breast cancer and colon cancer.

ADVANTAGE - (I) effectively eliminated and inhibit the growth of precancerous lesions and neoplasms, but without the severe side effects associated with non-steroidal inflammatory drugs (NSAIDs).

Dwg.0/0

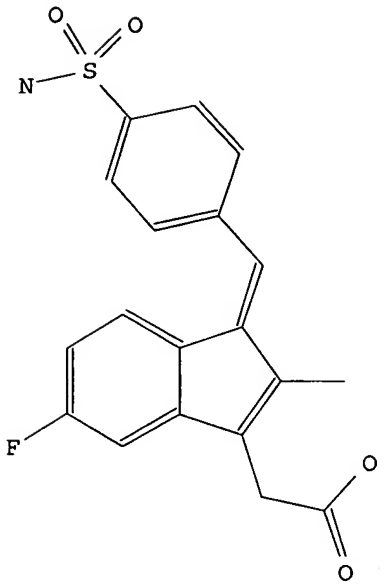
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-A02; B07-D04C; B07-D09; B07-D12; B07-D13; B07-E03; B07-F01; B10-B01; B10-B02; B10-B03; B10-B04; B10-C04; B10-E02; B10-E04; B14-A01; B14-A02; B14-C03; B14-C09B; B14-D05C; B14-G01B; B14-G02D; B14-H01; B14-J01A3; B14-J01A4; B14-S01
ABEX UPTX: 19991207

SPECIFIC COMPOUNDS - (I) is e.g. (Z)-5-fluoro-2-methyl-1-(4-chlorobenzylidene)-3-indenylacetic acid of formula (Ia).

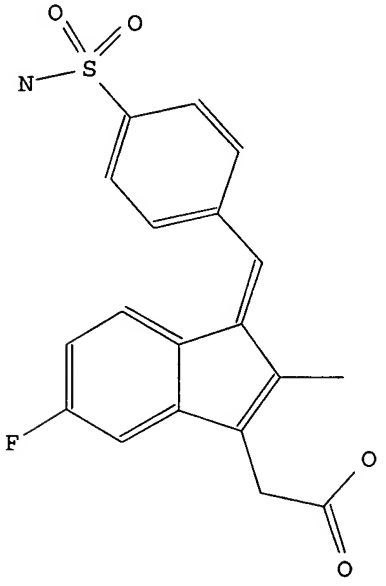
ADMINISTRATION - Administration is oral or rectal.

EXAMPLE - 5-Fluoro-2-methyl-3-indenylacetic acid (15 g), 3,4,5-trimethoxybenzaldehyde (12.39 g) and sodium methoxide (13.0 g), were heated in methanol (200 ml) at 60 degrees C under N2 with stirring for 6 hours. After cooling, the mixture was poured into ice-water (750 ml) and acidified with 2.5 N hydrochloric acid. The resulting solid was collected and triturated with ether to give (Z)-5-fluoro-2-methyl-1-(4-chlorobenzylidene)-3-indenylacetic acid (Ia), m.pt. = 166-169 degrees C.

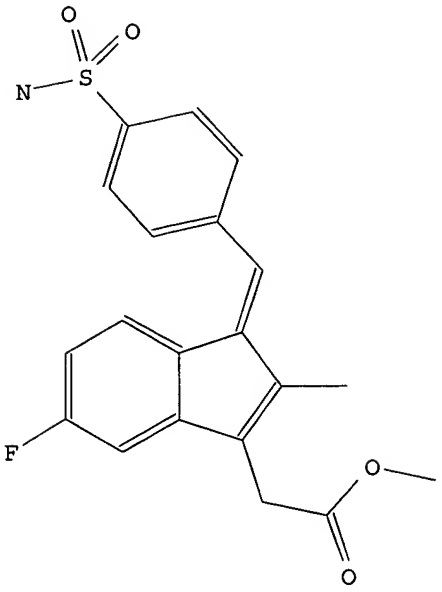
DCSE 240765-0-0-0
CN.S [6-Fluoro-2-methyl-3-(4-sulfamoyl-benzylidene)-3H-inden-1-yl]-acetic acid
SDCN RA0UIT



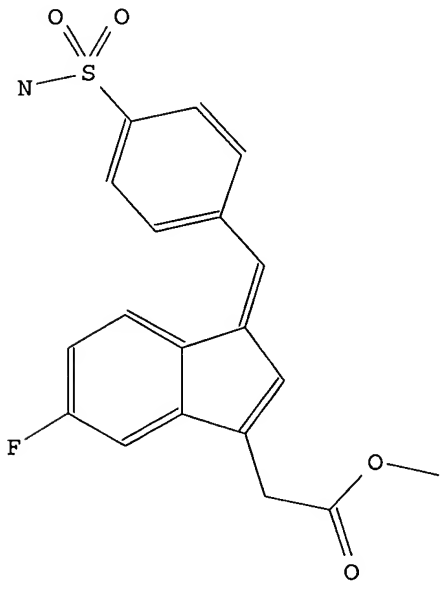
DCSE 240765-0-0-0
CN.S [6-Fluoro-2-methyl-3-(4-sulfamoyl-benzylidene)-3H-inden-1-yl]-acetic acid
SDCN RA0UIT



DCSE 240766-0-0-0
CN.S [6-Fluoro-2-methyl-3-(4-sulfamoyl-benzylidene)-3H-inden-1-yl]-acetic acid methyl ester
SDCN RA0UIU



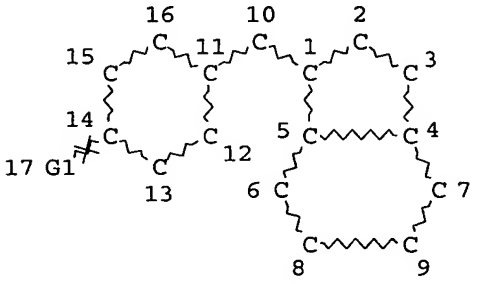
DCSE 240780-0-0-0
CN.S [6-Fluoro-3-(4-sulfamoyl-benzylidene)-3H-inden-1-yl]-acetic acid methyl ester
SDCN RA0UJ9



```
=> d his l84

     (FILE 'HCAPLUS, USPATFULL, USPAT2, TOXCENTER, IFICDB, IFIPAT, IFIUDB'
     ENTERED AT 11:32:24 ON 27 MAR 2006)
L84          38 S L50 NOT L83

=> d que stat l84
L15              STR
```

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VAR G1=18/19
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  19

STEREO ATTRIBUTES: NONE
L16 (       856)SEA FILE=REGISTRY SSS FUL L15
L17              STR
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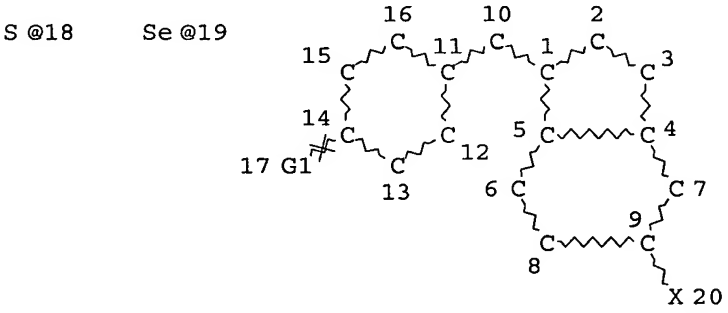



```
VAR G1=18/19
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

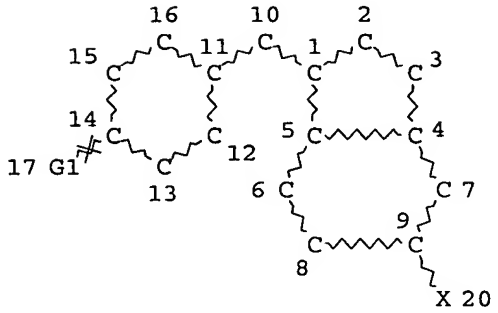
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  20

STEREO ATTRIBUTES: NONE
```

```
L18 (       622)SEA FILE=REGISTRY SUB=L16 SSS FUL L17
L19 (        69)SEA L19
L20 (        46)DUP REM L19 (23 DUPLICATES REMOVED)
L21 (        20)SEA FILE=HCAPLUS L20
L22 (        20)SEA FILE=HCAPLUS L21 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
               MY<2004 OR REVIEW/DT)
L23 (        23)SEA FILE=USPATFULL L20
L24 (        22)SEA FILE=USPATFULL L23 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
               MY<2004 OR REVIEW/DT)
L25 (         0)SEA FILE=USPAT2 L20
L26 (         0)SEA FILE=USPAT2 L25 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
               MY<2004 OR REVIEW/DT)
L27 (         2)SEA FILE=TOXCENTER L20
L28 (         2)SEA FILE=TOXCENTER L27 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
               MY<2004 OR REVIEW/DT)
L29 (         1)SEA FILE=IFICDB L20
L30 (         1)SEA FILE=IFICDB L29 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
               MY<2004 OR REVIEW/DT)
L31 (         0)SEA FILE=IFIPAT L20
L32 (         0)SEA FILE=IFIPAT L31 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
               MY<2004 OR REVIEW/DT)
L33 (         0)SEA FILE=IFIUDB L20
L34 (         0)SEA FILE=IFIUDB L33 AND (AY<2004 OR PY<2004 OR PRY<2004 OR
               MY<2004 OR REVIEW/DT)
L35 (        45)SEA L20 AND (AY<2004 OR PY<2004 OR PRY<2004 OR MY<2004 OR
               REVIEW/DT)
L36 (        20)SEA FILE=HCAPLUS L20
L37          20 SEA FILE=HCAPLUS L36 OR L22
L38 (        23)SEA FILE=USPATFULL L20
L39          23 SEA FILE=USPATFULL L38 OR L24
L40 (         0)SEA FILE=USPAT2 L20
L41 (         0)SEA FILE=USPAT2 L40 OR L26
L42 (         2)SEA FILE=TOXCENTER L20
L43           2 SEA FILE=TOXCENTER L42 OR L28
L44 (         1)SEA FILE=IFICDB L20
L45           1 SEA FILE=IFICDB L44 OR L30
L46 (         0)SEA FILE=IFIPAT L20
L47 (         0)SEA FILE=IFIPAT L46 OR L32
L48 (         0)SEA FILE=IFIUDB L20
L49 (         0)SEA FILE=IFIUDB L48 OR L34
L50          46 SEA L20 OR L35
L66             QUE  ABB=ON  PLU=ON  ?OXIDAS?
L67             QUE  ABB=ON  PLU=ON  ?NEURODEGEN? OR (NEURO(1W)DEGEN?) OR
                 (NEURON(3A)DEGEN?) OR ?ALZHEIM? OR ANTIALZHEIM? OR PARKI
                NSON? OR ANTIPARKINSON? OR (AMYTROPH?(3A)?SCLER?) OR STRO
                KE OR (HEART(1W)ATTACK) OR ?INFARCT? OR ?ISCHEM?
L68             QUE  ABB=ON  PLU=ON  ?CARDIO? OR ?PULMON? OR ?VASCUL? OR
                ?CORONAR? OR ?CARDIAC? OR ?IMMUN? OR AUTOIMMUN? OR AGING
                OR AGE
L69             QUE  ABB=ON  PLU=ON  MSRA OR MSRB OR (?METHIONIN?(5A)?RED
                UCTAS?)
L83           8 SEA L50 AND (L66/TI,IT,CC,CT,ST,STP OR L67/TI,IT,CC,CT,ST,STP
                OR L68/TI,IT,CC,CT,ST,STP OR L69/TI,IT,CC,CT,ST,STP)
L84          38 SEA L50 NOT L83


=> d que stat l55
L51             STR
```

S @18 Se @19



N 21

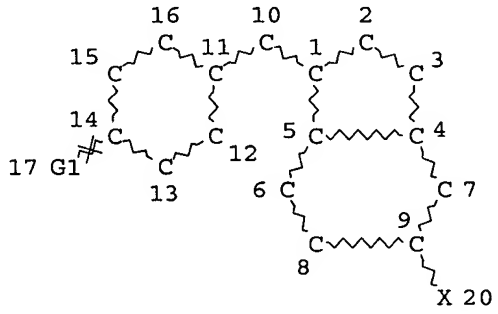
S 23

VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 21
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
L52 (0)SEA FILE=BEILSTEIN SSS FUL L51
L53 STR

S @18 Se @19



N 21

Se 23

VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 21
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

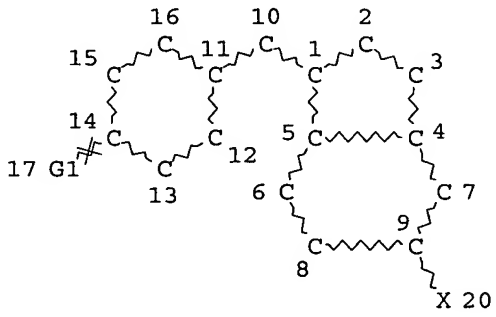
GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
L54 (0)SEA FILE=BEILSTEIN SSS FUL L53
L55 0 SEA FILE=BEILSTEIN ABB=ON PLU=ON L52 OR L54

=> d que stat l57
L56 STR

S @18 Se @19



N 21

VAR G1=18/19
NODE ATTRIBUTES:
NSPEC IS RC AT 18
NSPEC IS RC AT 19
NSPEC IS RC AT 21
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

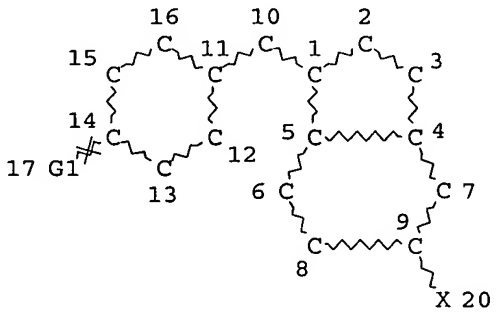
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE
L57 1 SEA FILE=CHEMINFORMRX SSS FUL L56 (2 REACTIONS)

100.0% DONE 452 VERIFIED 2 HIT RXNS 1 DOCS
SEARCH TIME: 00.00.16

=> d que stat l71
L60 STR

S @18 Se @19



N 21

VAR G1=18/19
NODE ATTRIBUTES:

```
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
NSPEC   IS RC     AT  21
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  21

STEREO ATTRIBUTES: NONE
L61 (         31)SEA FILE=WPIX SSS FUL L60
L62           10 SEA FILE=WPIX ABB=ON  PLU=ON  L61/DCR
L64           10 SEA FILE=WPIX ABB=ON  PLU=ON  (RADE8D/DCN OR RAD07D/DCN OR
                 RAEL7G/DCN OR RAEL7H/DCN OR RAEL7I/DCN OR RAIATA/DCN OR
                 RAK8R3/DCN OR RA0UIT/DCN OR RA0UIU/DCN OR RA0UJ9/DCN OR
                 RA3O0J/DCN OR RA5TOA/DCN OR RA5TOD/DCN OR RA5TOF/DCN OR
                 RA5TOH/DCN OR RA5TOI/DCN OR RA5TOJ/DCN OR RA5TOK/DCN OR
                 RA5TO4/DCN OR RA5TO5/DCN OR RA5TO6/DCN OR RA5TO7/DCN OR
                 RA5TO8/DCN OR RA7NPU/DCN OR RA7NPV/DCN OR RA7NPW/DCN OR
                 RA7NPX/DCN OR RA7NPY/DCN OR RA7NPZ/DCN OR RA7NQ0/DCN OR
                 RA7NQ1/DCN)
L65           10 SEA FILE=WPIX ABB=ON  PLU=ON  L62 OR L64
L70            9 SEA FILE=WPIX ABB=ON  PLU=ON  L65 AND ((?OXIDAS?/BIX) OR
                 (?NEURODEGEN?/BIX OR (NEURO/BIX(1W)DEGEN?/BIX) OR (NEURON/BIX(3
                 A)DEGEN?/BIX) OR ?ALZHEIM?/BIX OR ANTIALZHEIM?/BIX OR PARKINSON
                 ?/BIX OR ANTIPARKINSON?/BIX OR (AMYTROPH?/BIX(3A)?SCLER?/BIX)
                 OR STROKE/BIX OR (HEART/BIX(1W)ATTACK/BIX) OR ?INFARCT?/BIX OR
                 ?ISCHEM?/BIX) OR (?CARDIO?/BIX OR ?PULMON?/BIX OR ?VASCUL?/BIX
                 OR ?CORONAR?/BIX OR ?CARDIAC?/BIX OR ?IMMUN?/BIX OR AUTOIMMUN?/
                 BIX OR AGING/BIX OR AGE/BIX) OR (MSRA/BIX OR MSRB/BIX OR
                 (?METHIONIN?/BIX(5A)?REDUCTAS?/BIX)))
L71            1 SEA FILE=WPIX ABB=ON  PLU=ON  L65 NOT L70


=> d his l74

     (FILE 'MEDLINE, BIOSIS, PASCAL, JICST-EPLUS, CABA, LIFESCI, EMBASE,
     DRUGU, DRUGB, VETU, VETB, SCISEARCH, CONF, CONFSCI, DISSABS' ENTERED AT
     11:14:20 ON 27 MAR 2006)


=> d que stat l75
L6                STR
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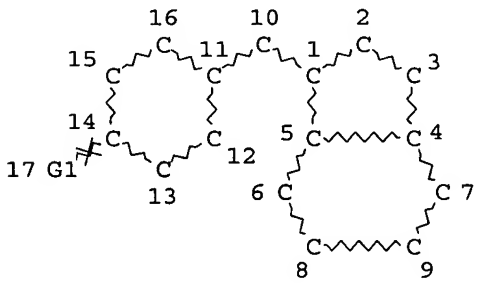


S @18 Se @19

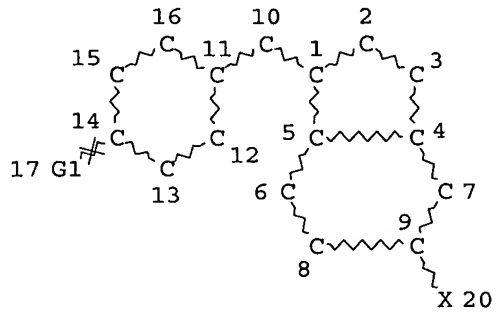
```
VAR G1=18/19
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
```

```
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  19

STEREO ATTRIBUTES: NONE
L7  (       856)SEA FILE=REGISTRY SSS FUL L6
L8              STR

S @18    Se @19
```




```
VAR G1=18/19
NODE ATTRIBUTES:
NSPEC   IS RC     AT  18
NSPEC   IS RC     AT  19
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  20

STEREO ATTRIBUTES: NONE
L9  (       622)SEA FILE=REGISTRY SUB=L7 SSS FUL L8
L10 (        50)SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND S>1
L11 (         0)SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND SE>1
L12 (         0)SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND S/ELS AND SE/ELS
L13 (        50)SEA FILE=REGISTRY ABB=ON  PLU=ON  (L10 OR L11 OR L12)
L14          29 SEA FILE=REGISTRY ABB=ON  PLU=ON  L13 AND N/ELS
L74             SEL  PLU=ON  L14 1- CHEM :      30 TERMS
L75           0 SEA L74


=> dup rem l84 l55 l57 l71 l75
L55 HAS NO ANSWERS
L75 HAS NO ANSWERS
DUPLICATE IS NOT AVAILABLE IN 'BEILSTEIN, CHEMINFORMRX, CONF'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
FILE 'HCAPLUS' ENTERED AT 11:45:10 ON 27 MAR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPATFULL' ENTERED AT 11:45:10 ON 27 MAR 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'TOXCENTER' ENTERED AT 11:45:10 ON 27 MAR 2006
COPYRIGHT (C) 2006 ACS
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FILE 'IFICDB' ENTERED AT 11:45:10 ON 27 MAR 2006
COPYRIGHT (C) 2006 IFI CLAIMS(R) Patent Services (IFI)

FILE 'CHEMINFORMRX' ENTERED AT 11:45:10 ON 27 MAR 2006
COPYRIGHT (C) FIZ-CHEMIE BERLIN

FILE 'WPIX' ENTERED AT 11:45:10 ON 27 MAR 2006
COPYRIGHT (C) 2006 THE THOMSON CORPORATION
PROCESSING COMPLETED FOR L84
PROCESSING COMPLETED FOR L55
PROCESSING COMPLETED FOR L57
PROCESSING COMPLETED FOR L71
PROCESSING COMPLETED FOR L75
L90           40 DUP REM L84 L55 L57 L71 L75 (0 DUPLICATES REMOVED)
                 ANSWERS '1-15' FROM FILE HCAPLUS
                 ANSWERS '16-35' FROM FILE USPATFULL
                 ANSWERS '36-37' FROM FILE TOXCENTER
                 ANSWER '38' FROM FILE IFICDB
                 ANSWER '39' FROM FILE CHEMINFORMRX
                 ANSWER '40' FROM FILE WPIX

=> file stnguide
FILE 'STNGUIDE' ENTERED AT 11:45:17 ON 27 MAR 2006
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Mar 24, 2006 (20060324/UP).
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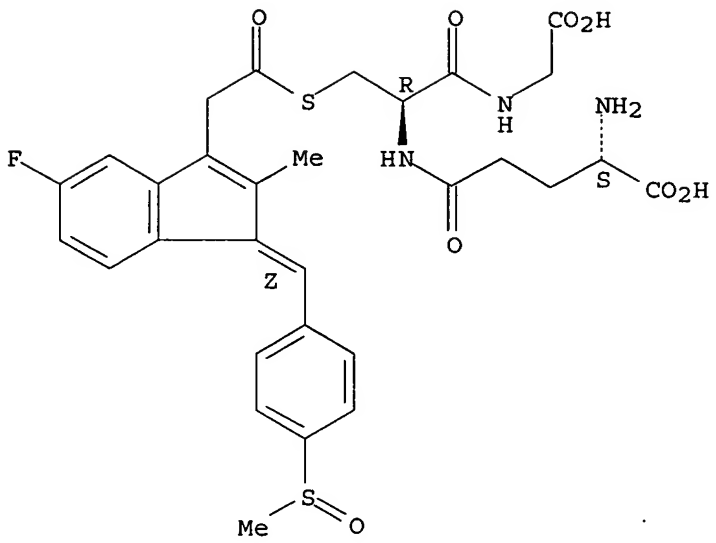
=> => d ibib ed ab hitstr
YOU HAVE REQUESTED DATA FROM FILE 'CHEMINFORMRX, WPIX, HCAPLUS, USPATFULL, TOXCENTER, IFICDB' - CONTINUE? (Y)/N:y

L90 ANSWER 1 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:415065 HCAPLUS
DOCUMENT NUMBER: 139:377104
TITLE: Exploration of in vitro pro-drug activation and futile cycling by glutathione S-transferases: thiol ester hydrolysis and inhibitor maturation
AUTHOR(S): Ibarra, Catherine; Grillo, Mark P.; Lo Bello, Mario; Nucettelli, Marzia; Bammler, Theo K.; Atkins, William M.
CORPORATE SOURCE: Department of Medicinal Chemistry, University of Washington, Seattle, WA, 98195-7610, USA
SOURCE: Archives of Biochemistry and Biophysics (**2003**), 414(2), 303-311
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 30 May 2003
AB In addition to glutathione (GSH) conjugating activity, glutathione S-transferases (GSTs) catalyze "reverse" reactions, such as the hydrolysis of GSH thiol esters. Reverse reactions are of interest as potential tumor-directed pro-drug activation strategies and as mechanisms for tissue redistribution of carboxylate-containing drugs. However, the mechanism and specificity of GST-mediated GSH thiol ester hydrolysis are uncharacterized. Here, the GSH thiol esters of ethacrynic acid (E-SG) and several nonsteroidal antiinflammatory agents have been tested as substrates with human GSTs. The catalytic hydrolysis of these thiol esters appears to be a general property of GSTs. The hydrolysis of the thiol ester of E-SG was studied further with GSTA1-1 and GSTP1-1, as a model pro-drug with several possible fates for the hydrolysis products: competitive inhibition, covalent enzyme adduction, and sequential metabolism In contrast to hydrolysis rates, significant isoform-dependent differences in the subsequent fate of the products ethacrynic acid and GSH were observed At low [E-SG], only the GSTP1-1 efficiently catalyzed sequential metabolism, via a dissociative mechanism.
IT **623150-28-7**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prodrug/substrate; mechanism and specificity of thiol ester pro-drug activation by human glutathione S-transferases)
RN 623150-28-7 HCAPLUS
CN Glycine, L-γ-glutamyl-S-[[(1Z)-5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-inden-3-yl]acetyl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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YOU HAVE REQUESTED DATA FROM FILE 'CHEMINFORMRX, WPIX, HCAPLUS, USPATFULL, TOXCENTER, IFICDB' - CONTINUE? (Y)/N:y

L90 ANSWER 2 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:1227 HCAPLUS
DOCUMENT NUMBER: 138:66667
TITLE: Methods for identifying compounds for inhibiting of neoplastic lesions, and pharmaceutical compositions containing such compounds
INVENTOR(S): Pamukcu, Rifat; Piazza, Gary A.
PATENT ASSIGNEE(S): Cell Pathways, Inc., USA
SOURCE: U.S., 53 pp., Cont.-in-part of U. S. Ser. No. 46,739.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6500610	B1	20021231	US 1999-414625	19991008 <--
US 5858694	A	19990112	US 1997-866027	19970530 <--
CA 2238283	AA	19981130	CA 1998-2238283	19980520 <--
CA 2238283	C	20020820		
TW 591111	B	20040611	TW 1998-87108072	19980525 <--
CZ 295868	B6	20051116	CZ 1998-1651	19980528 <--
NO 9802477	A	19981201	NO 1998-2477	19980529 <--
AU 9869794	A1	19981210	AU 1998-69794	19980529 <--
AU 709666	B2	19990902		
JP 11094823	A2	19990409	JP 1998-150033	19980529 <--
JP 3053381	B2	20000619		

ZA 9804646	A	19991129	ZA 1998-4646	19980529 <--
JP 2000198746	A2	20000718	JP 2000-44184	19980529 <--
AT 198771	E	20010215	AT 1998-304247	19980529 <--
ES 2132055	T3	20010501	ES 1998-304247	19980529 <--
IL 124699	A1	20030212	IL 1998-124699	19980529 <--
CN 1224761	A	19990804	CN 1998-102044	19980601 <--
CN 1122110	B	20030924		
HK 1012196	A1	20010412	HK 1998-113546	19981216 <--
US 6156528	A	20001205	US 1998-216070	19981219 <--
JP 2000028601	A2	20000128	JP 1999-189615	19990702 <--
JP 3234818	B2	20011204		
US 2003004093	A1	20030102	US 2002-40776	20020107 <--
US 2003064421	A1	20030403	US 2002-253849	20020924 <--
US 2003190686	A1	20031009	US 2002-252983	20020924 <--
PRIORITY APPLN. INFO.:			US 1997-866027	A2 19970530 <--
			US 1998-46739	A2 19980324 <--
			JP 1998-150033	A3 19980529 <--
			US 1998-216070	A2 19981219 <--
			US 1999-414625	A1 19991008 <--
			US 2000-602980	B1 20000623 <--
			US 2000-664035	B1 20000918 <--

ED Entered STN: 02 Jan 2003

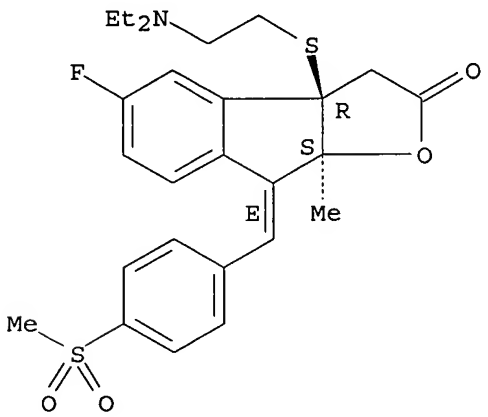
AB The invention provides pharmaceutical compns. containing compds. for the treatment of neoplasia in mammals. The phosphodiesterase inhibitory activity of a compound is determined along with cyclooxygenase inhibitory activity. Growth inhibitory and apoptosis inducing effects on cultured tumor cells are also determined Compds. that exhibit phosphodiesterase inhibition, growth inhibition and apoptosis induction, but preferably not substantial prostaglandin inhibitory activity, are desirable for the treatment of neoplasia.

IT **177982-86-4 266689-09-2 266689-11-6**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor agent identification methods, and pharmaceutical compns.)

RN 177982-86-4 HCAPLUS

CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (3aR,8E,8aS)-rel- (9CI) (CA INDEX NAME)

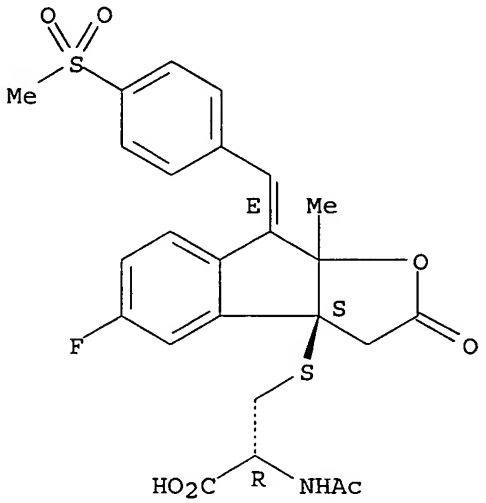
Relative stereochemistry.
Double bond geometry as shown.



RN 266689-09-2 HCAPLUS

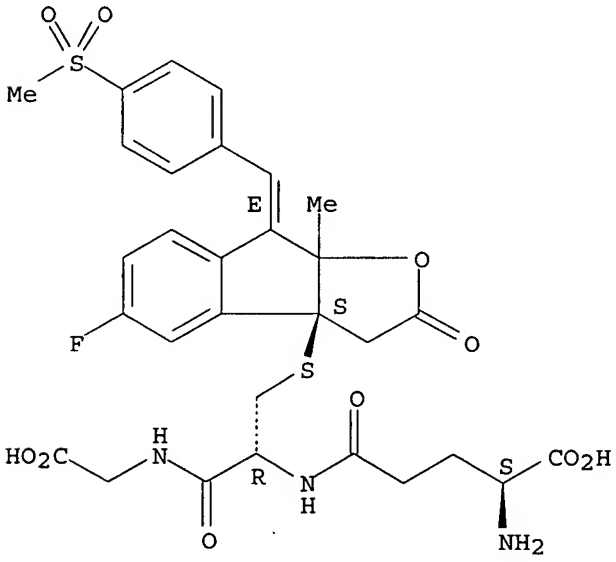
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 266689-11-6 HCAPLUS
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 263 THERE ARE 263 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

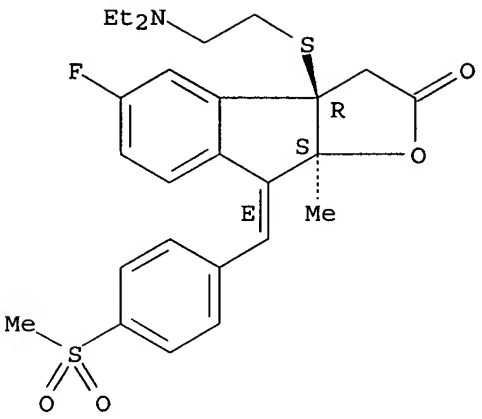
L90 ANSWER 3 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:780619 HCAPLUS
DOCUMENT NUMBER: 135:339217
TITLE: Method for treating a patient with neoplasia by treatment with a topoisomerase I inhibitor and a cGMP-specific phosphodiesterase inhibitor
INVENTOR(S): Pamukcu, Rifat; Lobacki, Joseph
PATENT ASSIGNEE(S): Cell Pathways, Inc., USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001078651	A2	20011025	WO 2001-US11865	20010412 <--
WO 2001078651	A3	20020314		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001055322	A5	20011030	AU 2001-55322	20010412 <--
EP 1278519	A2	20030129	EP 2001-928470	20010412 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-548135 A 20000412 <--
WO 2001-US11865 W 20010412 <--

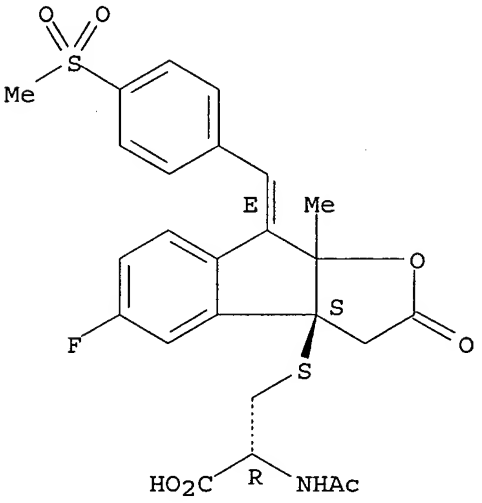
ED Entered STN: 26 Oct 2001
AB The invention provides a method for treating a patient with neoplasia by an adjuvant therapy that includes treatment with a topoisomerase I inhibitor and a cGMP-specific phosphodiesterase inhibitor. Isolation and characterization of phosphodiesterase activity from cancer cells is also described.
IT **177982-86-4 266689-09-2 266689-11-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topoisomerase I inhibitor and cGMP-specific phosphodiesterase inhibitor for neoplasia treatment)
RN 177982-86-4 HCAPLUS
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (3aR,8E,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



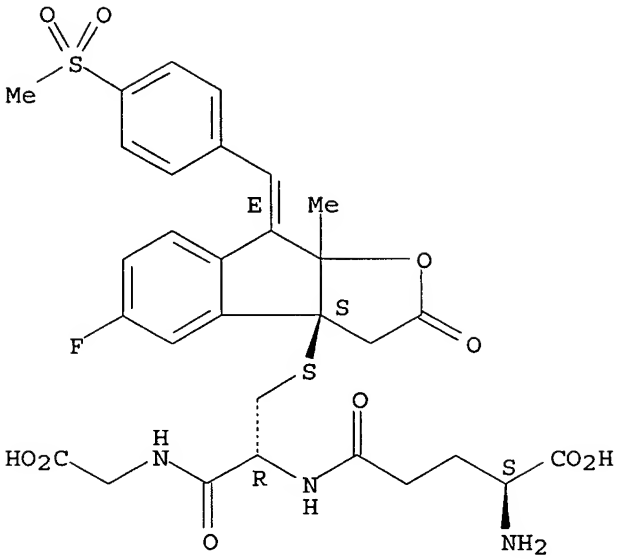
RN 266689-09-2 HCAPLUS
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 266689-11-6 HCAPLUS
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L90 ANSWER 4 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:661250 HCAPLUS
DOCUMENT NUMBER: 135:221272
TITLE: Method for treating a patient with neoplasia by treatment with a vinca alkaloid derivative
INVENTOR(S): Pamukcu, Rifat; Lobacki, Joseph
PATENT ASSIGNEE(S): Cell Pathways, Inc., USA
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001064210	A1	20010907	WO 2001-US5562	20010221 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6555547	B1	20030429	US 2000-515714	20000228 <--
PRIORITY APPLN. INFO.:			US 2000-515714 A	20000228 <--

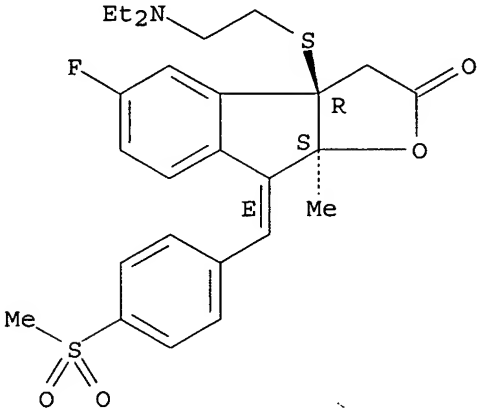
ED Entered STN: 10 Sep 2001
AB This invention provides a method for treating a patient with neoplasia by an adjuvant therapy that includes treatment with an antineoplastic vinca alkaloid derivative combined with a cyclic GMP-specific phosphodiesterase inhibitor. This invention also relates to packaged pharmaceutical compns. that are provided together with written materials describing the use of a cyclic GMP-specific phosphodiesterase inhibitor in combination with a vinca alkaloid derivative for the treatment of cancer and precancerous

lesions.

IT **177982-86-4 177983-07-2 177983-08-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for treating a patient with neoplasia by treatment with a vinca alkaloid derivative in combination with a cGMP phosphodiesterase inhibitor in relation to cyclooxygenase and protein kinase G and β-catenins)

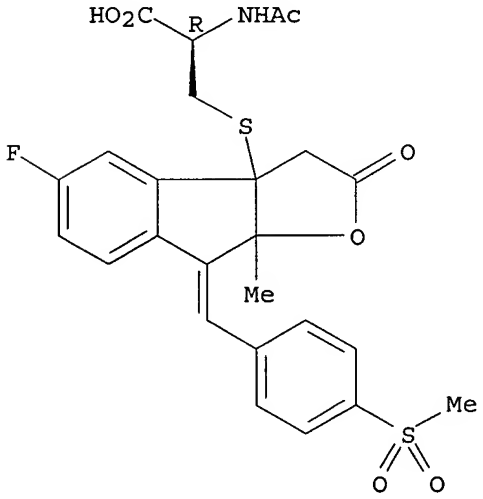
RN 177982-86-4 HCAPLUS
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (3aR,8E,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



RN 177983-07-2 HCAPLUS
CN L-Cysteine, N-acetyl-S-[5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

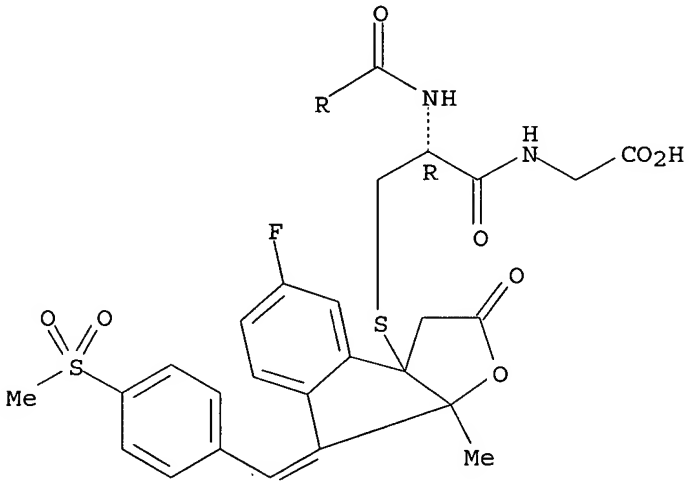
Absolute stereochemistry.
Double bond geometry unknown.



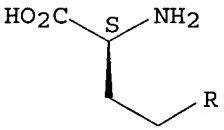
RN 177983-08-3 HCAPLUS
CN Glycine, L-γ-glutamyl-S-[5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



PAGE 2-A



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 5 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:335251 HCAPLUS
DOCUMENT NUMBER: 132:343299
TITLE: Method for treating a patient with neoplasia with an anthracycline antibiotic and a cGMP-specific phosphodiesterase inhibitor
INVENTOR(S): Pamukcu, Rifat; Menander, Kerstin B.
PATENT ASSIGNEE(S): Cell Pathways, Inc., USA
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2000027404	A1	20000518	WO 1999-US26717	19991112 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1131076	A1	20010912	EP 1999-963888	19991112 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002529418	T2	20020910	JP 2000-580633	19991112 <--
US 2003130210	A1	20030710	US 2002-274709	20021021 <--
PRIORITY APPLN. INFO.:			US 1998-190907	A2 19981112 <--
			WO 1999-US26717	W 19991112 <--
			US 2000-632561	B1 20000804 <--

ED Entered STN: 19 May 2000

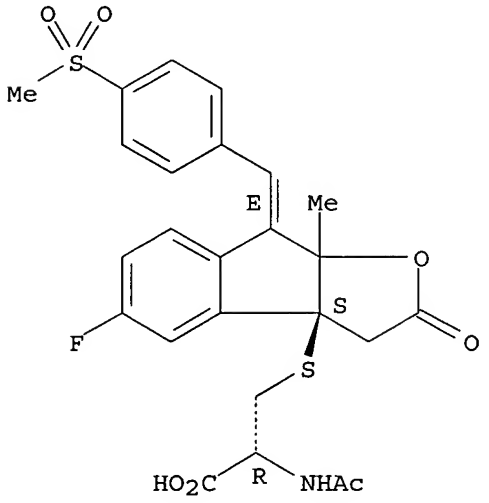
AB A method for treating a patient with neoplasia is provided which employs an anthracycline antibiotic and a cGMP-specific phosphodiesterase inhibitor.

IT **266689-09-2 266689-11-6 268545-30-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anthracycline antibiotic and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)

RN 266689-09-2 HCAPLUS

CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

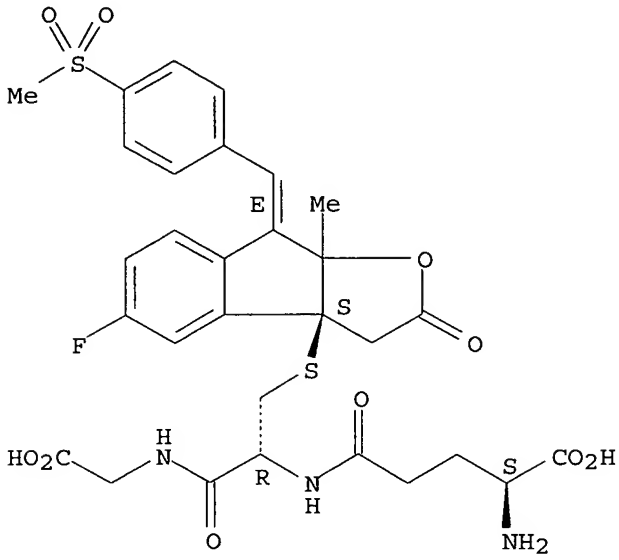


RN 266689-11-6 HCAPLUS

CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-

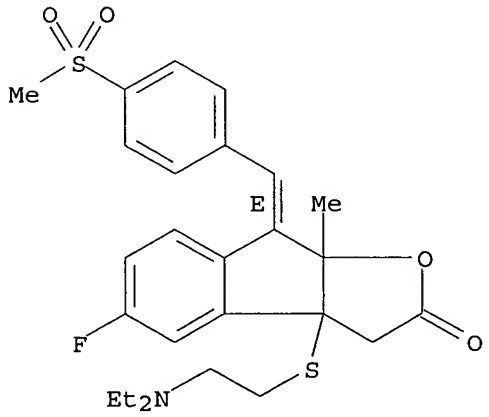
b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 HCAPLUS
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

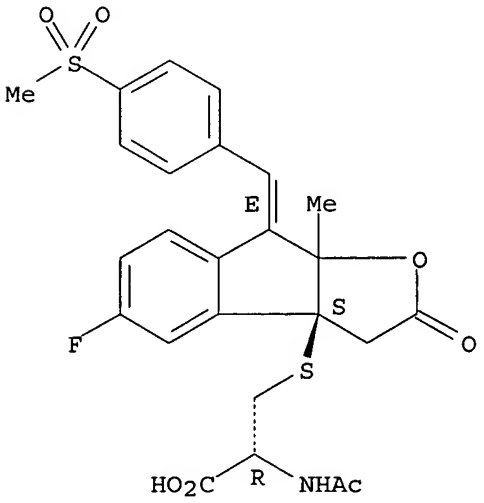
L90 ANSWER 6 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:335250 HCAPLUS
DOCUMENT NUMBER: 132:343298
TITLE: Method for treating a patient with neoplasia with a pyrimidine analog and a cGMP-specific phosphodiesterase inhibitor

INVENTOR(S): Pamukcu, Rifat; Menander, Kerstin B.
PATENT ASSIGNEE(S): Cell Pathways, Inc., USA
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000027403	A1	20000518	WO 1999-US26628	19991112 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002022586	A1	20020221	US 2000-734633	20001212 <--
PRIORITY APPLN. INFO.:			US 1998-190343	A2 19981112 <--
			WO 1999-US26628	A 19991112 <--

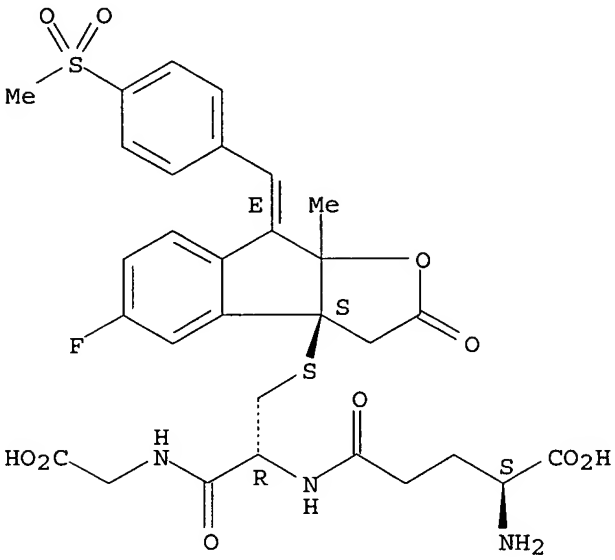
ED Entered STN: 19 May 2000
AB A method for treating a patient with neoplasia is provided which employs a pyrimidine analog and a cGMP-specific phosphodiesterase inhibitor.
IT **266689-09-2 266689-11-6 268545-30-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pyrimidine analog and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)
RN 266689-09-2 HCAPLUS
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



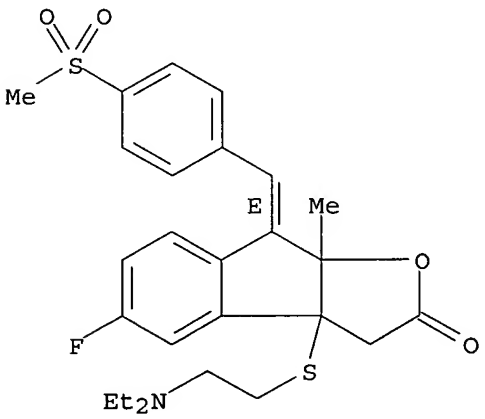
RN 266689-11-6 HCAPLUS
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 HCAPLUS
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 7 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:335240 HCAPLUS

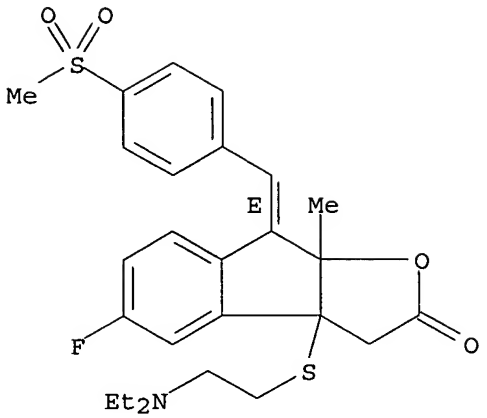
DOCUMENT NUMBER: 132:343297
TITLE: Method for treating a patient with neoplasia with a platinum coordination complex and a cGMP-specific phosphodiesterase inhibitor
INVENTOR(S): Pamukcu, Rifat; Menander, Kerstin B.
PATENT ASSIGNEE(S): Cell Pathways, Inc., USA
SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000027391	A1	20000518	WO 1999-US27006	19991112 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6235782	B1	20010522	US 1998-190830	19981112 <--
EP 1131069	A1	20010912	EP 1999-958979	19991112 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002529412	T2	20020910	JP 2000-580620	19991112 <--
US 2001012858	A1	20010809	US 2001-777395	20010206 <--
US 6359002	B2	20020319		
US 2002091157	A1	20020711	US 2002-39154	20020103 <--
US 2002137722	A1	20020926	US 2002-38634	20020103 <--
US 6472420	B2	20021029		
US 2003113382	A1	20030619	US 2002-228700	20020827 <--
US 6869944	B2	20050322		

PRIORITY APPLN. INFO.:		
US 1998-190830	A2	19981112 <--
WO 1999-US27006	W	19991112 <--
US 2001-777359	A3	20010206 <--
US 2001-777395	A3	20010206 <--
US 2002-39154	B1	20020103 <--

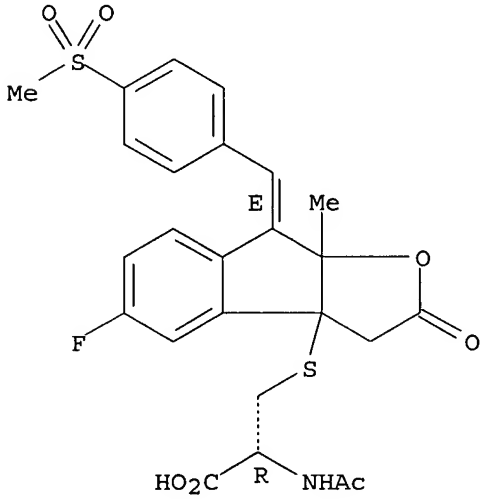
ED Entered STN: 19 May 2000
AB A method for treating a patient with neoplasia is provided which employs a platinum coordination complex and a cGMP-specific phosphodiesterase inhibitor.
IT **268545-30-8 268545-31-9 268545-32-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(platinum coordination complex and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)
RN 268545-30-8 HCAPLUS
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



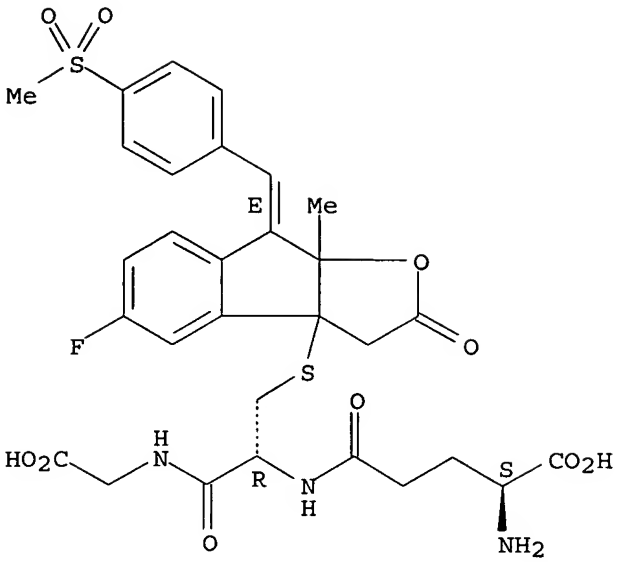
RN 268545-31-9 HCAPLUS
CN L-Cysteine, N-acetyl-S-[(8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-32-0 HCAPLUS
CN Glycine, L-γ-glutamyl-S-[(8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 8 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:335174 HCAPLUS
DOCUMENT NUMBER: 132:343296
TITLE: Method for treating a patient with neoplasia with a paclitaxel derivative and a cGMP-specific phosphodiesterase inhibitor
INVENTOR(S): Pamukcu, Rifat; Menander, Kerstin B.
PATENT ASSIGNEE(S): Cell Pathways, Inc., USA
SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000027194	A1	20000518	WO 1999-US27002	19991112 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6235776	B1	20010522	US 1998-190637	19981112 <--
EP 1128727	A1	20010905	EP 1999-965805	19991112 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002529376	T2	20020910	JP 2000-580444	19991112 <--
US 2001021720	A1	20010913	US 2001-777359	20010206 <--
US 6365627	B2	20020402		

PRIORITY APPLN. INFO.: US 1998-190637 A2 19981112 <--
WO 1999-US27002 W 19991112 <--

ED Entered STN: 19 May 2000

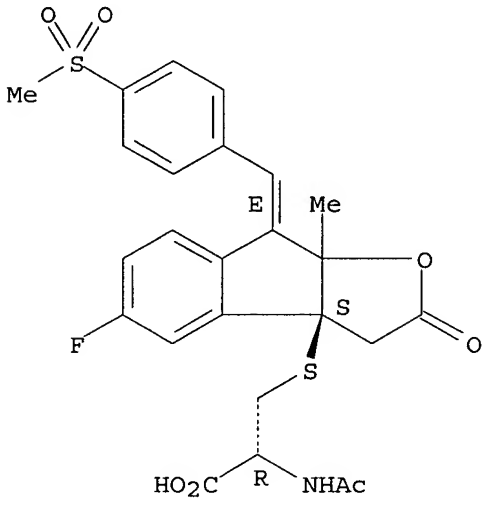
AB A method for treating a patient with neoplasia is provided which employs a paclitaxel derivative and a cGMP-specific phosphodiesterase inhibitor.

IT **266689-09-2 266689-11-6 268545-30-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(paclitaxel derivative and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)

RN 266689-09-2 HCAPLUS

CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

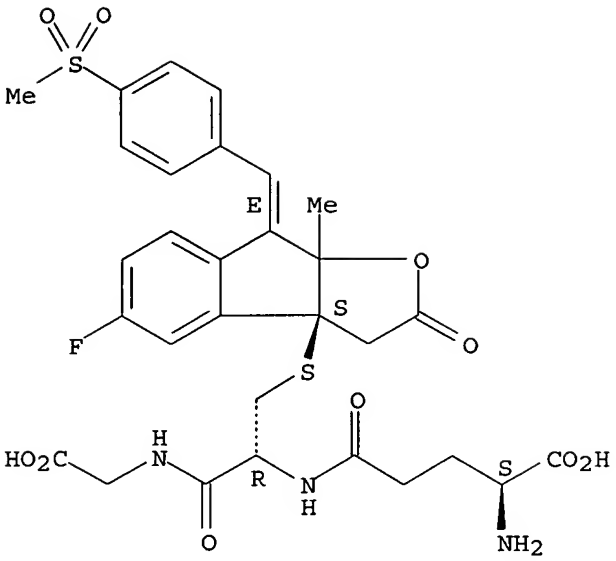
Absolute stereochemistry.
Double bond geometry as shown.



RN 266689-11-6 HCAPLUS

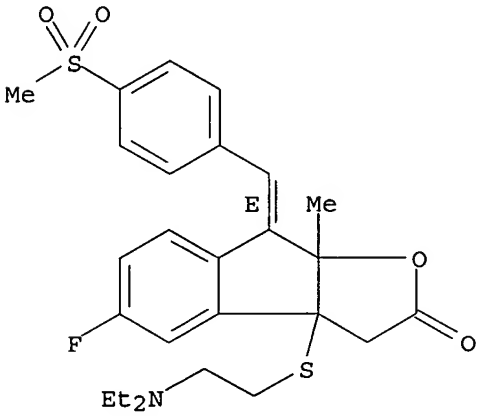
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 HCAPLUS
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 9 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:335173 HCAPLUS
DOCUMENT NUMBER: 132:343295
TITLE: Method for treating a patient with neoplasia with a gonadotropin releasing hormone analog and a cGMP-specific phosphodiesterase inhibitor
INVENTOR(S): Alila, Hector; Pamukcu, Rifat; Menander, Kerstin B.
PATENT ASSIGNEE(S): Cell Pathways, Inc., USA
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000027193	A1	20000518	WO 1999-US26716	19991112 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002193286	A1	20021219	US 2002-136140	20020430 <--
US 2003220252	A1	20031127	US 2003-377213	20030301 <--
PRIORITY APPLN. INFO.:			US 1998-190030	A2 19981112 <--
			US 2000-718113	B1 20001120 <--
			US 2001-968207	B1 20011002 <--
			US 2002-136140	B1 20020430 <--

ED Entered STN: 19 May 2000

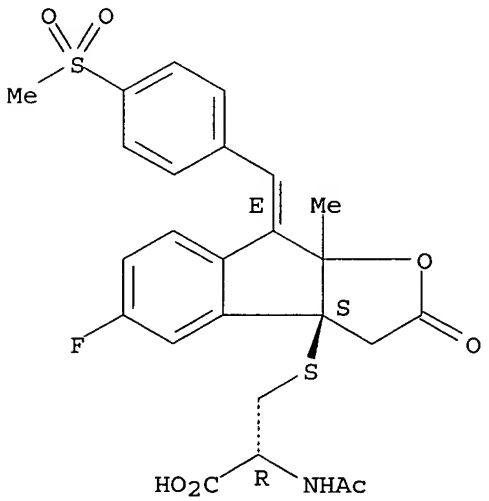
AB A method for treating a patient with neoplasia is provided which employs a gonadotropin-releasing hormone analog and a cGMP-specific phosphodiesterase inhibitor.

IT **266689-09-2 266689-11-6 268545-30-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gonadotropin releasing hormone analog and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)

RN 266689-09-2 HCAPLUS

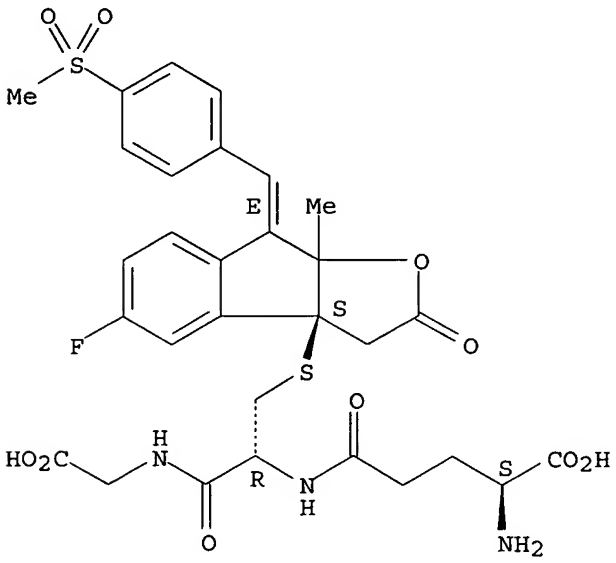
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



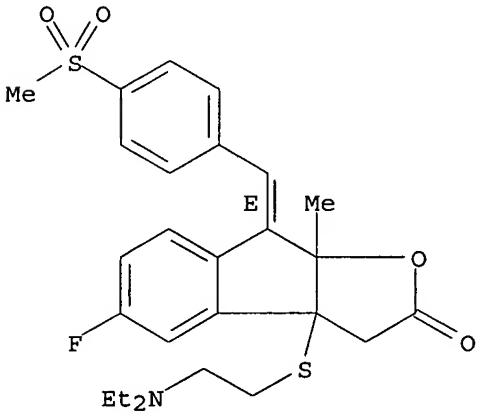
RN 266689-11-6 HCAPLUS
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 HCAPLUS
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 10 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:290577 HCAPLUS

DOCUMENT NUMBER: 132:329928
TITLE: Cyclooxygenase inhibition- and phosphodiesterase inhibition-based methods for identifying antineoplastic compounds, and pharmaceutical compositions
INVENTOR(S): Liu, Li; Zhu, Bing; Han, Li; Thompson, Joseph W.; Pamukeu, Rifat; Piazza, Gary A.
PATENT ASSIGNEE(S): Cell Pathways, Inc., USA
SOURCE: Eur. Pat. Appl., 65 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 997145	A1	20000503	EP 1999-308129	19991014 <--
EP 997145	B1	20020327		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6200771	B1	20010313	US 1998-173375	19981015 <--
US 6130053	A	20001010	US 1999-366003	19990803 <--
US 2002009764	A1	20020124	US 1999-414628	19991008 <--
CA 2284853	AA	20000415	CA 1999-2284853	19991014 <--
NO 9904995	A	20000417	NO 1999-4995	19991014 <--
ZA 9906508	A	20000418	ZA 1999-6508	19991014 <--
AU 9954010	A1	20000420	AU 1999-54010	19991014 <--
AU 770308	B2	20040219		
EP 1161943	A2	20011212	EP 2001-119687	19991014 <--
EP 1161943	A3	20031210		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AT 214920	E	20020415	AT 1999-308129	19991014 <--
ES 2174573	T3	20021101	ES 1999-308129	19991014 <--
KR 2000029189	A	20000525	KR 1999-45451	19991015 <--
CN 1255379	A	20000607	CN 1999-121818	19991015 <--
TR 9902578	A2	20000621	TR 1999-9902578	19991015 <--
JP 2000186047	A2	20000704	JP 1999-330364	19991015 <--
US 2003109418	A1	20030612	US 2002-187762	20020702 <--
US 2003175833	A1	20030918	US 2002-251165	20020920 <--
US 2004009464	A1	20040115	US 2002-253629	20020924 <--
US 2005244914	A1	20051103	US 2005-176073	20050707 <--

PRIORITY APPLN. INFO.:

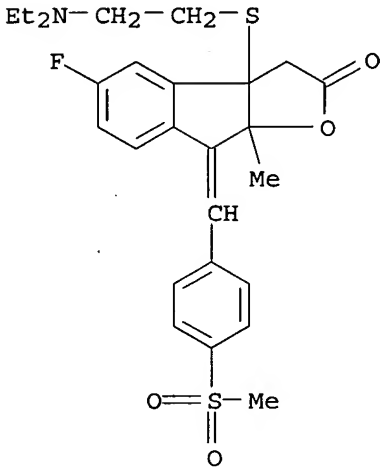
US 1998-173375	A	19981015 <--
US 1999-366003	A	19990803 <--
US 1999-414628	A	19991008 <--
US 1999-414626	B1	19991008 <--
EP 1999-308129	A3	19991014 <--
US 1999-420966	B1	19991020 <--
US 2002-253629	B3	20020924 <--

ED Entered STN: 05 May 2000
AB A pharmaceutical composition is disclosed for the treatment of neoplasia which comprises a pharmaceutically acceptable carrier and a compound selected by (1) determining the cyclooxygenase (COX) inhibitory activity of the compd; (2) determining the phosphodiesterase (PDE) inhibition activity of the compound, in which the PDE is characterized by (a) cGMP specificity over cAMP, (b) pos. cooperative kinetic behavior in the presence of cGMP substrate, (c) submicromolar affinity for cGMP, and (d) insensitivity to incubation with purified cGMP-dependent protein kinase; and (3) selecting the compound that has COX inhibitory activity lower than the PDE activity for treating

neoplasia. Also provided is a method for selecting a compound for the treatment of neoplasia which comprises (1) determining the COX inhibitory activity of the compound; (2) determining the PDE2 inhibition activity of the compound; and (3) selecting the compound that has COX inhibitory activity lower than the PDE activity for treating neoplasia. Isolation of a novel cGMP-specific PDE (appearing to be a novel conformation of PDE2) from neoplastic cells is described.

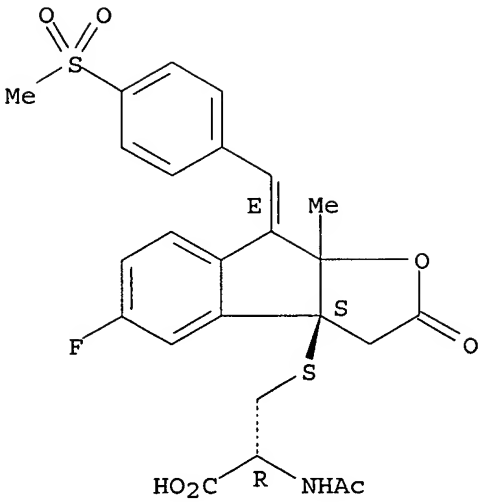
IT **178152-14-2 266689-09-2 266689-11-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase inhibition- and phosphodiesterase inhibition-based methods for identifying antineoplastic compds., and pharmaceutical compns.)

RN 178152-14-2 HCAPLUS
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-(9CI) (CA INDEX NAME)



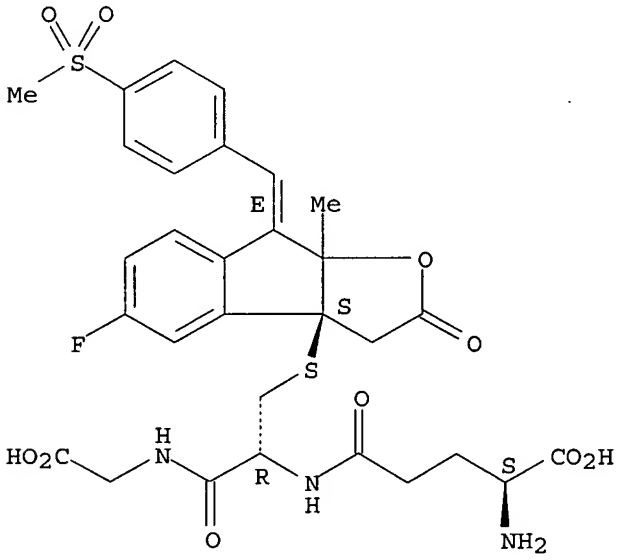
RN 266689-09-2 HCAPLUS
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 266689-11-6 HCAPLUS
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 11 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:457267 HCAPLUS
DOCUMENT NUMBER: 129:122563
TITLE: Preparation of lactone compounds for treating patient with precancerous lesions
INVENTOR(S): Gross, Paul; Sperl, Gerhard; Pamukcu, Rifat; Brendel,

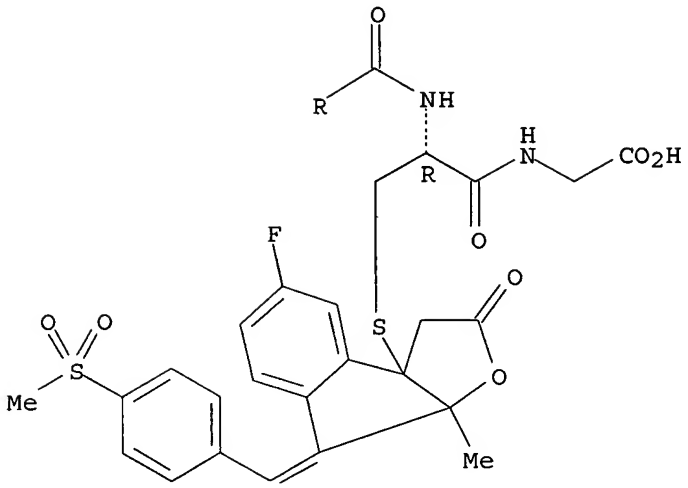
Klaus
PATENT ASSIGNEE(S): Cell Pathways, Inc., USA; University of Arizona
SOURCE: U.S., 21 pp., Cont.-in-part of U. S. Ser. No. 265,396.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5776962	A	19980707	US 1995-481601	19950607 <--
US 5696159	A	19971209	US 1994-265396	19940803 <--
CA 2172710	AA	19960215	CA 1995-2172710	19950731 <--
WO 9603987	A1	19960215	WO 1995-US8912	19950731 <--
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9532704	A1	19960304	AU 1995-32704	19950731 <--
AU 689305	B2	19980326		
EP 723442	A1	19960731	EP 1995-929312	19950731 <--
R: BE, CH, DE, ES, FR, GB, IT, LI, NL, SE				
JP 09506114	T2	19970617	JP 1995-506533	19950731 <--
PRIORITY APPLN. INFO.:			US 1994-265396 A2	19940803 <--
			US 1995-481601 A	19950607 <--
			WO 1995-US8912 W	19950731 <--

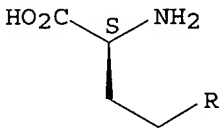
OTHER SOURCE(S): MARPAT 129:122563
ED Entered STN: 23 Jul 1998
AB The title compds. I [X = C, or R6X = N; R1, R2 = H, amino, etc.; or R1R2 = carbonyl, etc.; or R2R3 = double bond; R3 = H, halo, etc.; R4 = H, OH, etc.; R5 = H, OH, halo, etc.; R6 = H, alkyl, etc.; R7 = H, alkyl, etc.; R8, R9 = H, alkyl, OH, etc.; R10, R11 = H, halo, etc.; R12 = H, halo, etc.] are prepared Compds. of this invention in vitro showed IC50 values of 0.081 μM to 110 μM against the tumor HT-29 cell lines.
IT **177983-08-3P 210110-40-0P 210110-44-4P**
210110-45-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of lactone compds. for treating patient with precancerous lesions)
RN 177983-08-3 HCAPLUS
CN Glycine, L-γ-glutamyl-S-[5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A

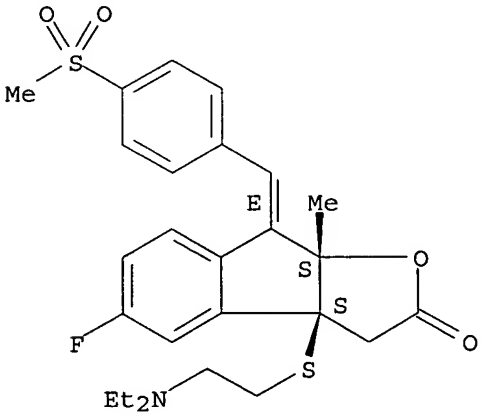


PAGE 2-A



RN 210110-40-0 HCAPLUS
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (3aR,8E,8aR)-rel- (9CI) (CA INDEX NAME)

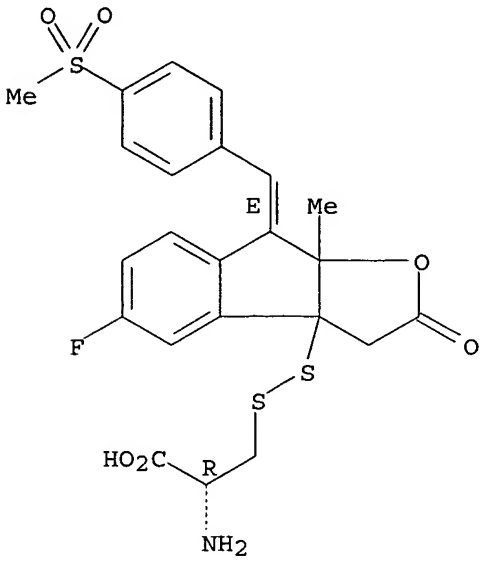
Relative stereochemistry.
Double bond geometry as shown.



RN 210110-44-4 HCAPLUS
CN L-Alanine, 3-[[(8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-

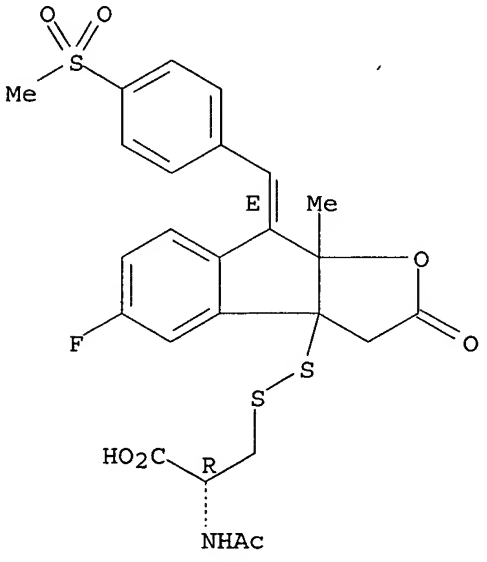
(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]dithio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 210110-45-5 HCAPLUS
CN L-Alanine, N-acetyl-3-[[(8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]dithio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 109 THERE ARE 109 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L90 ANSWER 12 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:379711 HCAPLUS
DOCUMENT NUMBER: 125:58302
TITLE: Preparation of oxotetrahydrofuran lactone antitumor agents
INVENTOR(S): Gross, Paul; Sperl, Gerhard; Pamukcu, Rifat; Brendel, Klaus
PATENT ASSIGNEE(S): Cell Pathways, Inc., USA; University of Arizona
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

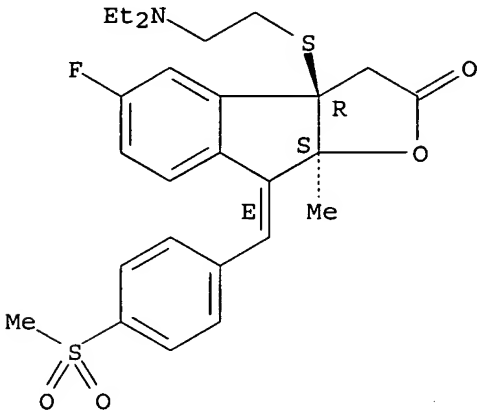
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9603987	A1	19960215	WO 1995-US8912	19950731 <--
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5696159	A	19971209	US 1994-265396	19940803 <--
US 5776962	A	19980707	US 1995-481601	19950607 <--
AU 9532704	A1	19960304	AU 1995-32704	19950731 <--
AU 689305	B2	19980326		
EP 723442	A1	19960731	EP 1995-929312	19950731 <--
R: BE, CH, DE, ES, FR, GB, IT, LI, NL, SE				
JP 09506114	T2	19970617	JP 1995-506533	19950731 <--

PRIORITY APPLN. INFO.:			
US 1994-265396	A	19940803 <--
US 1995-481601	A	19950607 <--
WO 1995-US8912	W	19950731 <--

OTHER SOURCE(S): MARPAT 125:58302
ED Entered STN: 02 Jul 1996
AB The title compds. [I; R1, R2 = H, amino, alkyl, alkoxy, azido, OH, halogen, acetoxyl, benzoxy, (un)substituted Ph; R3 = H, halogen, azido, alkyl, alkoxy, CN, OH, PhS, etc.; R4 = H, OH, halogen, alkyl, alkoxy, dialkylamino; R5 = H, OH, halogen, alkyl, alkoxy, dialkylamino, NH2; R6 = H, alkyl, HO, alkoxy, halogen, R7 = H, (un)substituted alkyl, Ph, etc.; R8, R9 = H, alkyl, HO, alkoxy, halogen; R10, R11 = H, haloge, alkoxy, alkyl; R12 = H, halogen, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, etc.; X = C, N (when X = N then R6 is absent)], useful in the treatment of precancerous lesions and neoplasms, are prepared Thus, (Z)-5-fluoro-2-methyl-1-(p-methylsulfinylbenzylidene)-3-indenylacetic acid was brominated with N-bromosuccinimide, producing racemic threo-(E)-1-bromo-1-(butan-1',4'-olido)-[3',4':1,2]-6-fluoro-2-methyl-3-(p-methylsulfinylbenzylidene)indane, m.p. 162°, which demonstrated a IC50 of 0.081 υM against the HT-29p136 human melanoma adenocarcinoma cell line.
IT **177982-86-4P 177983-06-1P 177983-07-2P**
177983-08-3P 178152-14-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of oxotetrahydrofuran lactone antitumor agents)

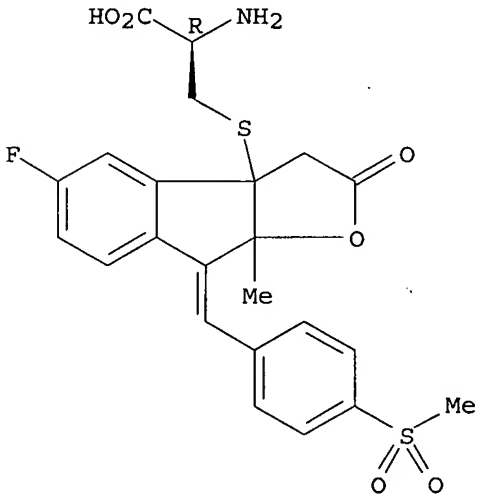
RN 177982-86-4 HCAPLUS
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (3aR,8E,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



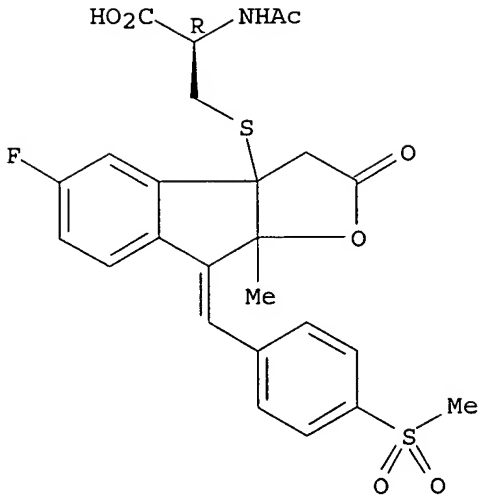
RN 177983-06-1 HCAPLUS
CN L-Cysteine, S-[5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 177983-07-2 HCAPLUS
CN L-Cysteine, N-acetyl-S-[5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

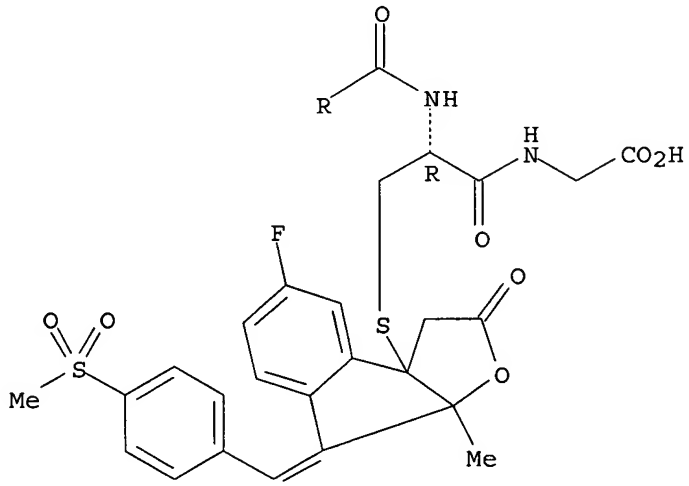
Absolute stereochemistry.
Double bond geometry unknown.



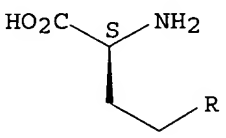
RN 177983-08-3 HCAPLUS
CN Glycine, L-γ-glutamyl-S-[5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

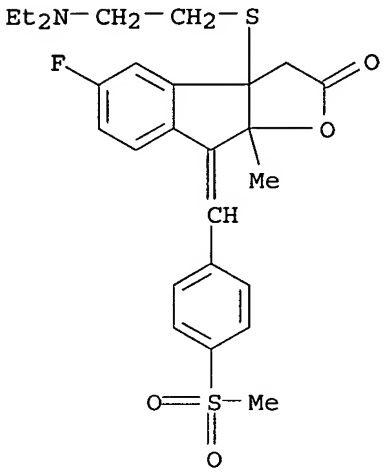
PAGE 1-A



PAGE 2-A



RN 178152-14-2 HCAPLUS
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-(9CI) (CA INDEX NAME)



L90 ANSWER 13 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:111681 HCAPLUS
DOCUMENT NUMBER: 112:111681
TITLE: Synthesis and biological evaluation of ω-(N,N,N-trialkylammonium)alkyl esters and thioesters of carboxylic acid nonsteroidal antiinflammatory agents
AUTHOR(S): Venuti, Michael C.; Young, John M.; Maloney, Patrick J.; Johnson, David; McGreevy, Kenneth
CORPORATE SOURCE: Inst. Bio-Org. Chem., Syntex Res., Palo Alto, CA, 94304, USA
SOURCE: Pharmaceutical Research (**1989**), 6(10), 867-73
CODEN: PHREEB; ISSN: 0724-8741
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 31 Mar 1990
AB A series of novel ω-(trialkylammonium)alkyl ester and thioester derivs. [RCOM(CH2)nN+R2R1 X-; R = Me, Et, Bu or R2 = (CH2)4, (CH2)5 or (CH2)2O, R1 = H, Me, or Et M = O or S, n = 2-6, X = I or Cl of 11 nonsteroidal antiinflammatory carboxylic acid agents (naproxen, ketorolac, indomethacin, ibuprofen, sulindac, ketoprofen, flufenamic acid, mefenamic acid, zomepirac, etodolac, and tifurac) was prepared and evaluated for their antiinflammatory, analgesic, and gastrointestinal erosive properties. In general, each prodrug retained the antiinflammatory activity characteristic of the corresponding parent drug but exhibited moderately to greatly reduced gastrointestinal erosive properties and significantly reduced analgetic potencies. This profile is likely due to a combination of factors including the rate of hydrolysis of the esters in the stomach, gut, and plasma, changes in the locus of absorption of the prodrug or nonsteroidal antiinflammatory drug (NSAID), and altered metabolic disposition patterns resulting from these changes. The results obtained from the compds. of this series indicate that esters of this general class

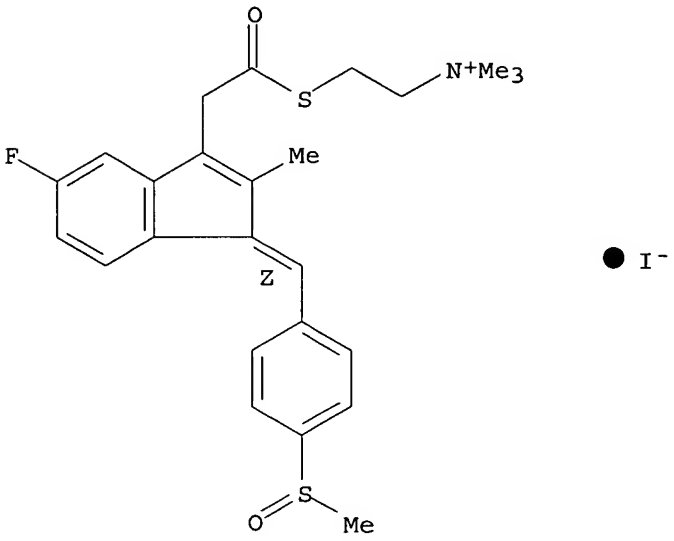
may offer a means to modulate both the aqueous/lipid solubility and the hydrolytic/enzymic cleavage indexes of NSAID prodrugs which potentially possess a more favorable therapeutic ratio of antiinflammatory to gastrointestinal erosive activities.

IT **125421-58-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and inflammation inhibiting activity of, as prodrug)

RN 125421-58-1 HCAPLUS

CN Ethanaminium, 2-[[[5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-inden-3-yl]acetyl]thio]-N,N,N-trimethyl-, iodide, (Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L90 ANSWER 14 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1983:470572 HCAPLUS
DOCUMENT NUMBER: 99:70572
TITLE: Pyridylalkyl thioesters and pharmaceutical preparations containing them
INVENTOR(S): Betzing, Hans; Graf, Erich; Leyck, Sigurd
PATENT ASSIGNEE(S): Nattermann, A., und Cie. G.m.b.H., Fed. Rep. Ger.
SOURCE: Ger. Offen., 15 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

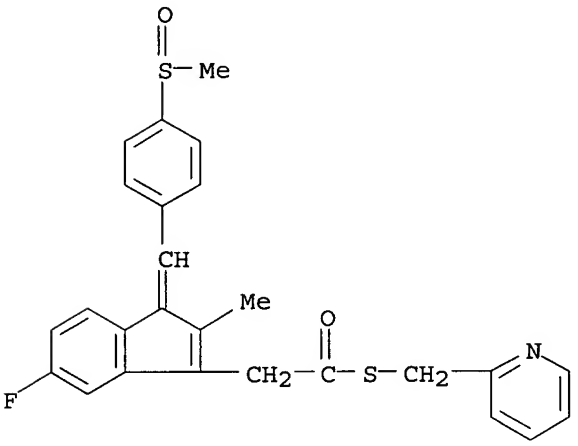
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3141473	A1	19830505	DE 1981-3141473	19811020 <--

PRIORITY APPLN. INFO.: DE 1981-3141473 19811020 <--
OTHER SOURCE(S): CASREACT 99:70572; MARPAT 99:70572
ED Entered STN: 12 May 1984
AB Pyridines I [R = H, halo, C1-3 alkyl or alkoxy; R1 = H, Me, Et; R2 = Ph, naphthyl, Bz, indenyl, which are (un)substituted with halo, C1-4 alkyl or alkoxy, PhO, Bz, Ph, halophenyl, MeSOC6H4CH; m = 0-1; n = 0-3] and their salts, useful as antithrombotics, antiarteriosclerotics, analgesics, and

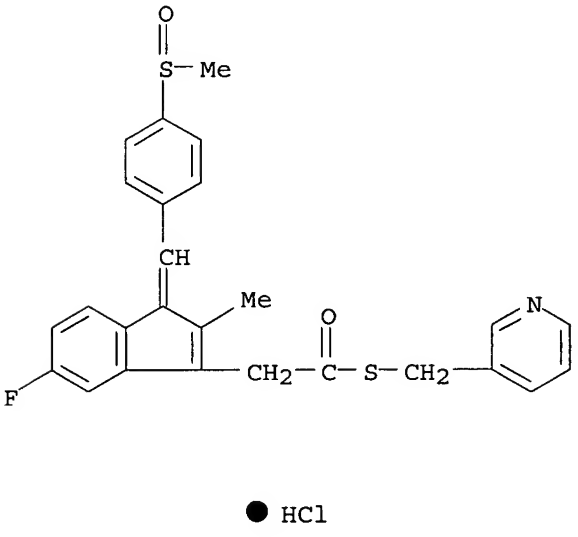
antiphlogistics (no data), were prepared 4-Me2CHCH2C6H4CHMeCO2H in CHCl3 was esterified with N,N'-dicyclohexylcarbodiimide and 2-(mercaptomethyl)pyridine in 30 h at 40-45° to give 78% the thiopropionate II.

IT **86657-14-9P 86657-23-0P 86657-24-1P**
86657-25-2P 86657-26-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 86657-14-9 HCAPLUS
CN 1H-Indene-3-ethanethioic acid, 5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-, S-(2-pyridinylmethyl) ester (9CI) (CA INDEX NAME)



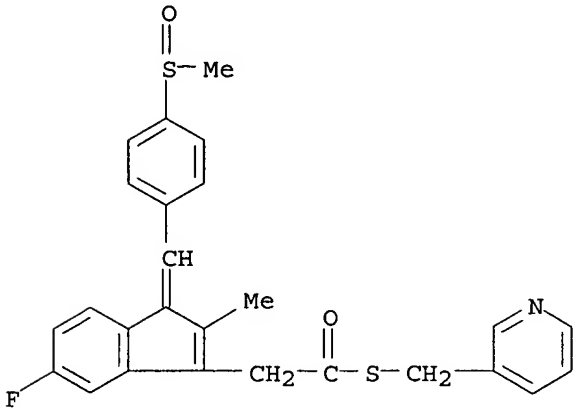
RN 86657-23-0 HCAPLUS
CN 1H-Indene-3-ethanethioic acid, 5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-, S-(3-pyridinylmethyl) ester, hydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 86657-24-1 HCAPLUS

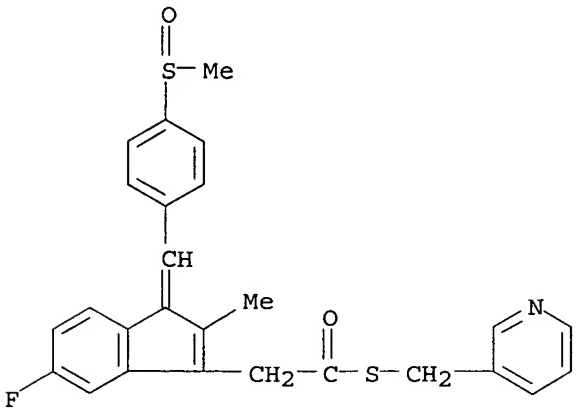
CN 1H-Indene-3-ethanethioic acid, 5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-, S-(3-pyridinylmethyl) ester (9CI) (CA INDEX NAME)



RN 86657-25-2 HCAPLUS
CN 1H-Indene-3-ethanethioic acid, 5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-, S-(3-pyridinylmethyl) ester, (2E)-2-butenedioate (2:1) (9CI) (CA INDEX NAME)

CM 1

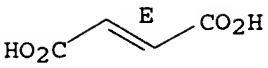
CRN 86657-24-1
CMF C26 H22 F N O2 S2



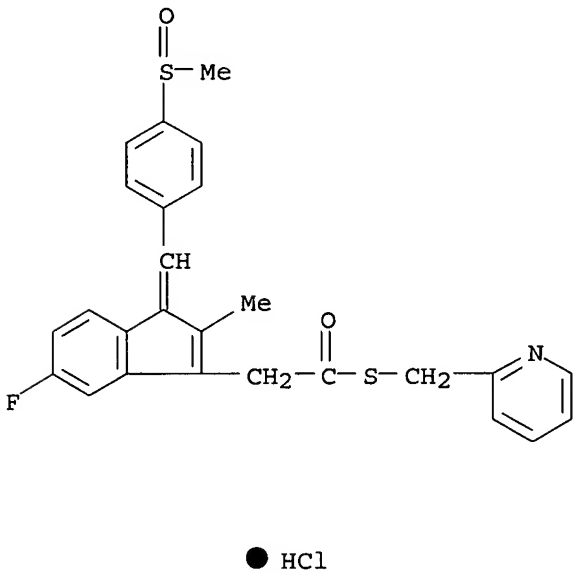
CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.



RN 86657-26-3 HCAPLUS
CN 1H-Indene-3-ethanethioic acid, 5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-, S-(2-pyridinylmethyl) ester, hydrochloride (9CI) (CA INDEX NAME)



● HCl

L90 ANSWER 15 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1972:526307 HCAPLUS
DOCUMENT NUMBER: 77:126307
TITLE: Indenylalkanoic acids
INVENTOR(S): Shen, Tsung-Ying; Jones, Howard; Fordice, Michael Walter
PATENT ASSIGNEE(S): Merck and Co., Inc.
SOURCE: Ger. Offen., 40 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2202728	A	19720803	DE 1972-2202728	19720120 <--
US 3737455	A	19730605	US 1971-108631	19710121 <--
NL 7200062	A	19720725	NL 1972-62	19720104 <--
AU 7237793	A1	19730712	AU 1972-37793	19720111 <--
CH 579036	A	19760831	CH 1972-373	19720111 <--
GB 1369543	A	19741009	GB 1972-2194	19720117 <--
FR 2122587	A5	19720901	FR 1972-2069	19720121 <--
FR 2122587	B1	19760416		

PRIORITY APPLN. INFO.: US 1971-108631 A 19710121 <--
ED Entered STN: 12 May 1984

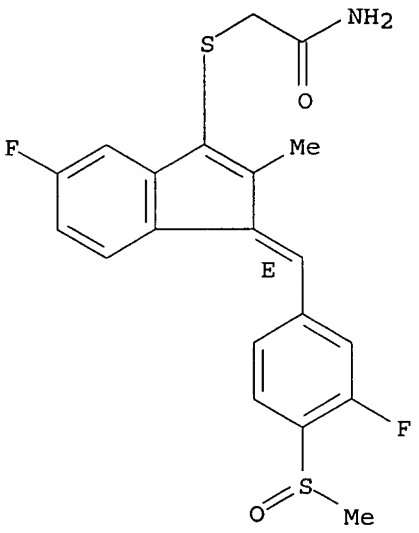
AB Antiinflammatory methylsulfinylbenzylideneindeneacetic acids (I, R = SOMe, R1 = H, OH, F; R2 = OH, OEt, OCMe3, OCH2OMe, OCH2CH2NEt2, NH2; R3 = F, allyloxy; R4 = F, H; X = O, S, NH, NMe, NCH2Ph) were prepared Thus di-Me 4,5-difluorophthalate was treated with EtCO2Et to give 5,6-difluoro-2-methylindan-1,3-dione, whose 3,3-ethylene ketal was treated with p-MeSC6H4CH2MgBr to give 5,6-difluoro-3,3-ethylenedioxy-2-methyl-1-(4-methylthiobenzylidene)indan (II) as a cis-trans mixture The cis-isomer of II was separated, the ketal group removed, treated with NaH, then BrCH2CO2Et to give I (R = SMe, R1 = H, R2 = OEt, R3 = R4 = F, X = O). Hydrolysis of the ester, followed by NaIO4 oxidation gave I (R = SOMe, R1 = H, R2 = OH, R3 = R4 = F, X = O).

IT **38185-43-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 38185-43-2 HCAPLUS

CN Acetamide, 2-[[5-fluoro-1-[[3-fluoro-4-(methylsulfinyl)phenyl]methylene]-2-methyl-1H-inden-3-yl]thio]-, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



=> d ibib ab hitstr 16-35
YOU HAVE REQUESTED DATA FROM FILE 'CHEMINFORMRX, WPIX, HCAPLUS, USPATFULL, TOXCENTER, IFICDB' - CONTINUE? (Y)/N:y

L90 ANSWER 16 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2005:280963 USPATFULL
TITLE: Methods for identifying compounds for inhibition of neoplastic lesions, and pharmaceutical compositions containing such compounds
INVENTOR(S): Liu, Li, Ambler, PA, UNITED STATES
Zhu, Bing, Mobile, AL, UNITED STATES
Li, Han, Yardley, PA, UNITED STATES
Thompson, W. Joseph, Doylestown, PA, UNITED STATES
Pamukcu, Rifat, Springhouse, PA, UNITED STATES
Piazza, Gary A., Doylestown, PA, UNITED STATES

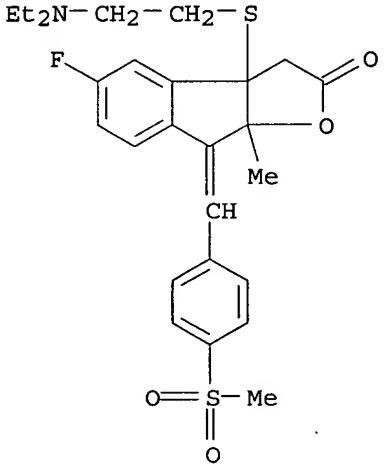
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005244914	A1	20051103
APPLICATION INFO.:	US 2005-176073	A1	20050707 (11)

RELATED APPLN. INFO.: Division of Ser. No. US 2002-253629, filed on 24 Sep 2002, ABANDONED Continuation of Ser. No. US 1999-414626, filed on 8 Oct 1999, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: OSI PHARMACEUTICALS, INC., 58 SOUTH SERVICE ROAD, MELVILLE, NY, 11747, US
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 2405
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides pharmaceutical compositions containing compounds for the treatment of neoplasia in mammals. The phosphodiesterase inhibitory activity of a compound is determined along with COX inhibitory activity. Growth inhibitory and apoptosis inducing effects on cultured tumor cells are also determined. Compounds that exhibit phosphodiesterase inhibiton, growth inhibition and apoptosis induction, but prefereably not substantial prostaglandin inhibitory activity, are desirable for the treatment of neoplasia.

IT **178152-14-2 266689-09-2 266689-11-6**
(cyclooxygenase inhibition- and phosphodiesterase inhibition-based methods for identifying antineoplastic compds., and pharmaceutical compns.)

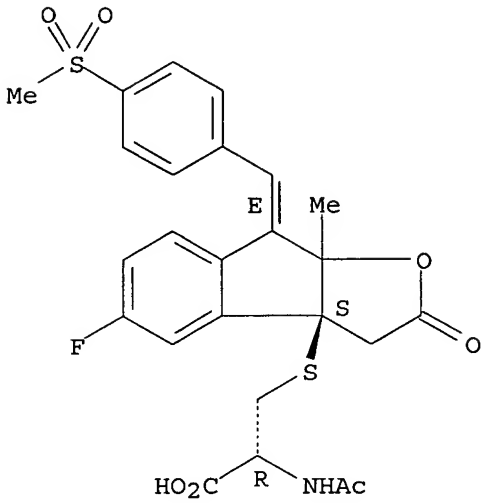
RN 178152-14-2 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]- (9CI) (CA INDEX NAME)



RN 266689-09-2 USPATFULL
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

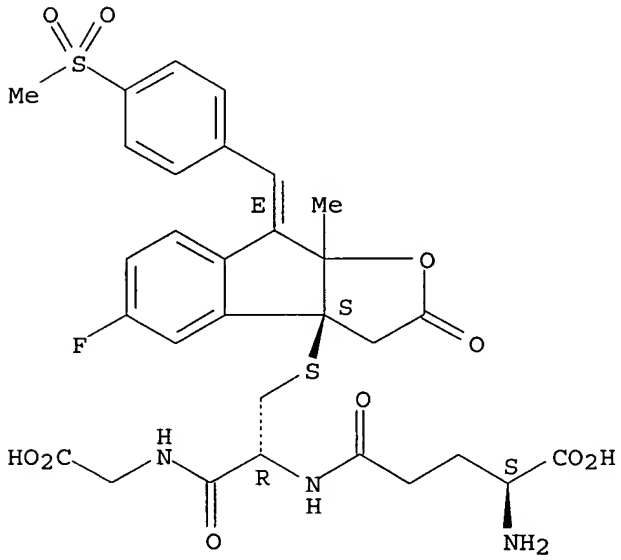
Absolute stereochemistry.

Double bond geometry as shown.



RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L90 ANSWER 17 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2004:12945 USPATFULL
TITLE: Methods for identifying compounds for inhibition of neoplastic lesions, and pharmacetical compositions containing such compounds
INVENTOR(S): Liu, Li, Ambler, PA, UNITED STATES
Zhu, Bing, Mobile, AL, UNITED STATES

Li, Han, Yardley, PA, UNITED STATES
Thompson, W. Joseph, Doylestown, PA, UNITED STATES
Pamukcu, Rifat, Springhouse, PA, UNITED STATES
Piazza, Gary A., Doylestown, PA, UNITED STATES

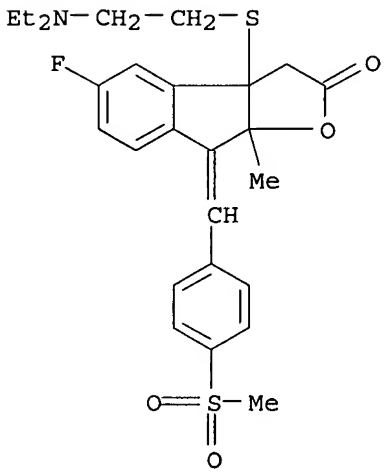
	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 2004009464	A1	20040115		
APPLICATION INFO.:	US 2002-253629	A1	20020924	(10)	<--

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-414626, filed on 8 Oct 1999, ABANDONED Continuation-in-part of Ser. No. US 1998-173375, filed on 15 Oct 1998, GRANTED, Pat. No. US 6200771
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Cell Pathways, Inc., 702 Electronic Dr., Horhsam, PA, 19044
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 2469
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides pharmaceutical compositions containing compounds for the treatment of neoplasia in mammals. The phosphodiesterase inhibitory activity of a compound is determined along with COX inhibitory activity. Growth inhibitory and apoptosis inducing effects on cultured tumor cells are also determined. Compounds that exhibit phosphodiesterase inhibiton, growth inhibition and apoptosis induction, but prefereably not substantial prostaglandin inhibitory activity, are desirable for the treatment of neoplasia.

IT **178152-14-2 266689-09-2 266689-11-6**
(cyclooxygenase inhibition- and phosphodiesterase inhibition-based methods for identifying antineoplastic compds., and pharmaceutical compns.)

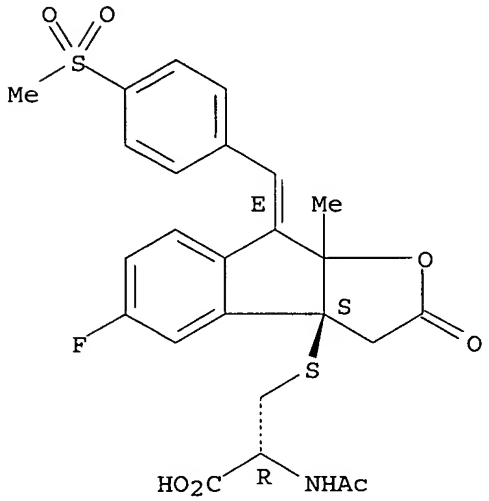
RN 178152-14-2 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]- (9CI) (CA INDEX NAME)



RN 266689-09-2 USPATFULL

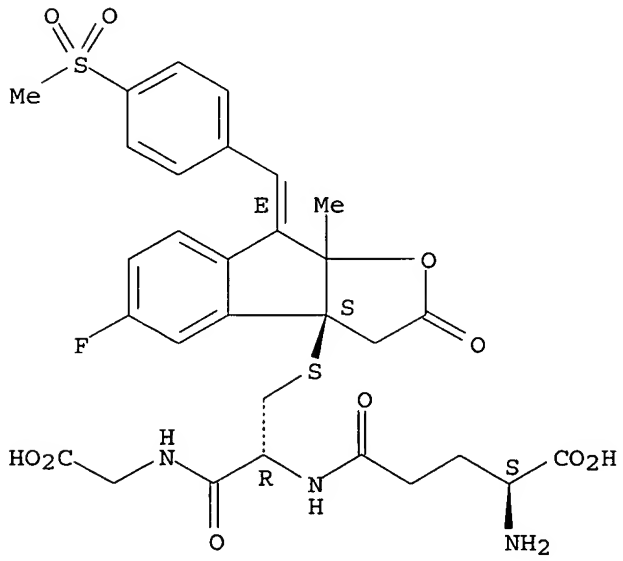
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L90 ANSWER 18 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2003:312647 USPATFULL

TITLE: Method for treating a patient with neoplasia by treatment with a gonadotropin releasing hormone analog

INVENTOR(S): Pamukcu, Rifat, Spring House, PA, UNITED STATES
Menander, Kerstin B., Meadowbrook, PA, UNITED STATES
Alila, Hector, North Wales, PA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003220252	A1	20031127	<--
APPLICATION INFO.:	US 2003-377213	A1	20030301 (10)	<--

RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-136140, filed on 30 Apr 2002, ABANDONED Continuation of Ser. No. US 2001-968207, filed on 2 Oct 2001, ABANDONED Continuation of Ser. No. US 2000-718113, filed on 20 Nov 2000, ABANDONED Continuation of Ser. No. US 1998-190030, filed on 12 Nov 1998, ABANDONED

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CELL PATHWAYS, INC, 702 ELECTRONIC DRIVE, HORSHAM, PA, 19044
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Page(s)
LINE COUNT: 1052
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

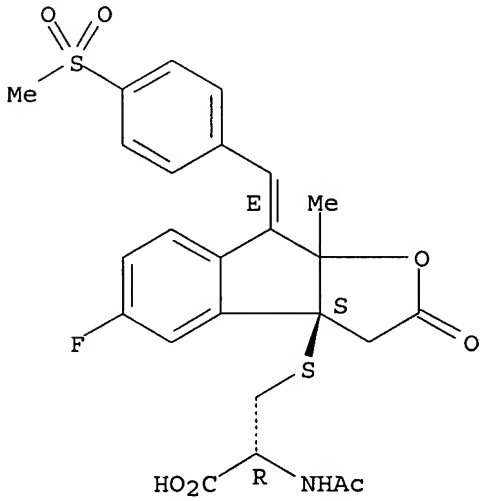
AB This invention provides a method for treating a patient with neoplasia by an adjuvant therapy that includes treatment with a gonadotropin-releasing hormone analog.

IT **266689-09-2 266689-11-6 268545-30-8**
(gonadotropin releasing hormone analog and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)

RN 266689-09-2 USPATFULL

CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

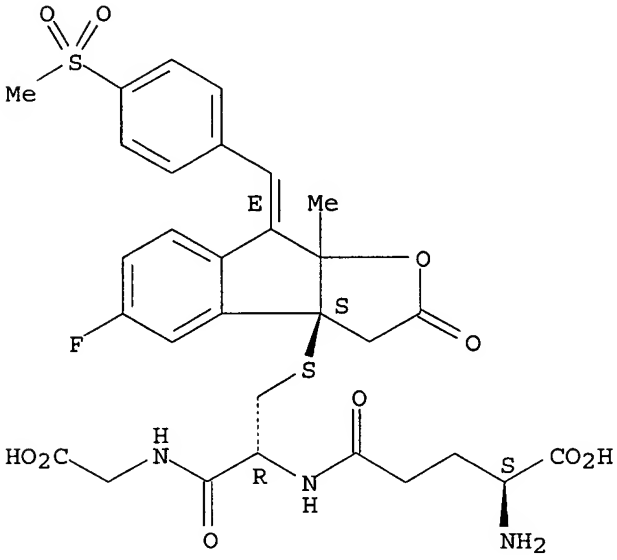
Absolute stereochemistry.
Double bond geometry as shown.



RN 266689-11-6 USPATFULL

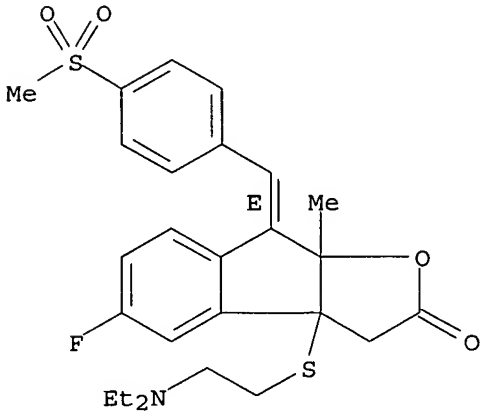
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L90 ANSWER 19 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2003:251047 USPATFULL
TITLE: Packaged pharmaceuticals and methods for causing compounds and pharmaceutical compositions to be used as inhibitors of neoplastic lesions
INVENTOR(S): Liu, Li, Ambler, PA, UNITED STATES

Zhu, Bing, Mobile, AL, UNITED STATES
Li, Han, Yardley, PA, UNITED STATES
Thompson, W. Joseph, Doylestown, PA, UNITED STATES
Pamukcu, Rifat, Spring House, PA, UNITED STATES
Piazza, Gary A., Doylestown, PA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003175833	A1	20030918	<--
APPLICATION INFO.:	US 2002-251165	A1	20020920 (10)	<--

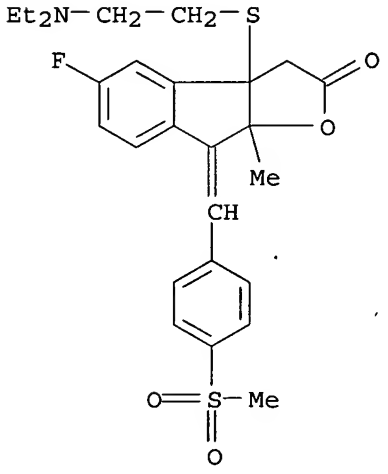
RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-420966, filed on 20 Oct 1999, ABANDONED Continuation of Ser. No. US 1998-173375, filed on 15 Oct 1998, GRANTED, Pat. No. US 6200771
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Cell Pathways, Inc., 702 Electronic Dr., Horsham, PA, 19044
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 2646
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides pharmaceutical compositions containing compounds for the treatment of neoplasia in mammals. The phosphodiesterase inhibitory activity of a compound is determined along with COX inhibitory activity. Growth inhibitory and apoptosis inducing effects on cultured tumor cells are also determined. Compounds that exhibit phosphodiesterase inhibiton, growth inhibition and apoptosis induction, but prefereably not substantial prostaglandin inhibitory activity, are desirable for the treatment of neoplasia.

IT **178152-14-2 266689-09-2 266689-11-6**
(cyclooxygenase inhibition- and phosphodiesterase inhibition-based methods for identifying antineoplastic compds., and pharmaceutical compns.)

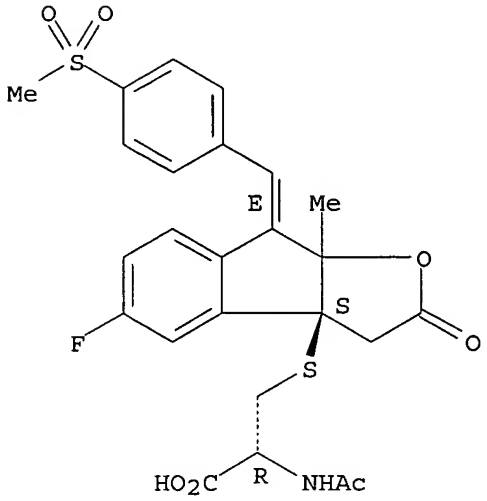
RN 178152-14-2 USPATFULL

CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-(9CI) (CA INDEX NAME)



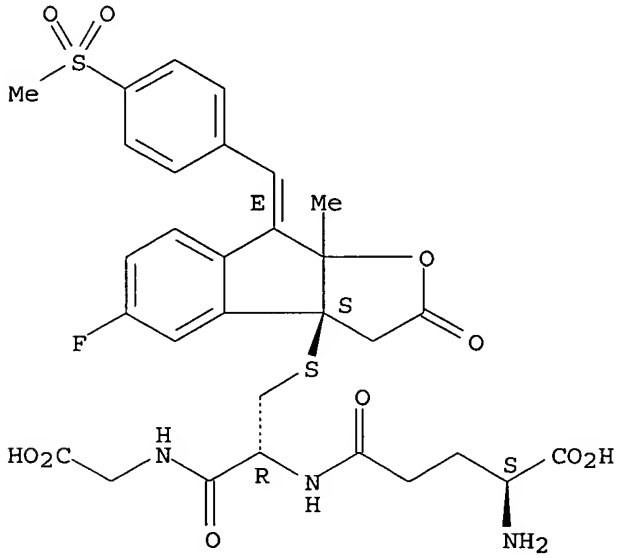
RN 266689-09-2 USPATFULL
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L90 ANSWER 20 OF 40 USPATFULL on STN

ACCESSION NUMBER: 2003:188417 USPATFULL
TITLE: Method for treating a patient with neoplasia by treatment with an anthracycline antibiotic
INVENTOR(S): Pamukcu, Rifat, Spring House, PA, UNITED STATES
Menander, Kerstin B., Meadowbrook, PA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003130210	A1	20030710	<--
APPLICATION INFO.:	US 2002-274709	A1	20021021 (10)	<--

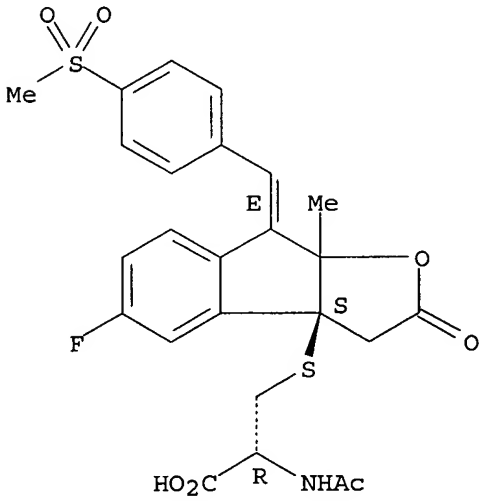
RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-632561, filed on 4 Aug 2000, ABANDONED Continuation of Ser. No. US 1998-190907, filed on 12 Nov 1998, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Robert W. Stevenson, 702 Electronic Dr, Horsham, PA, 19044
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Page(s)
LINE COUNT: 1102
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a method for treating a patient with neoplasia by an adjuvant therapy that includes treatment with an anthracycline antibiotic.

IT **266689-09-2 266689-11-6 268545-30-8**
(anthracycline antibiotic and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)

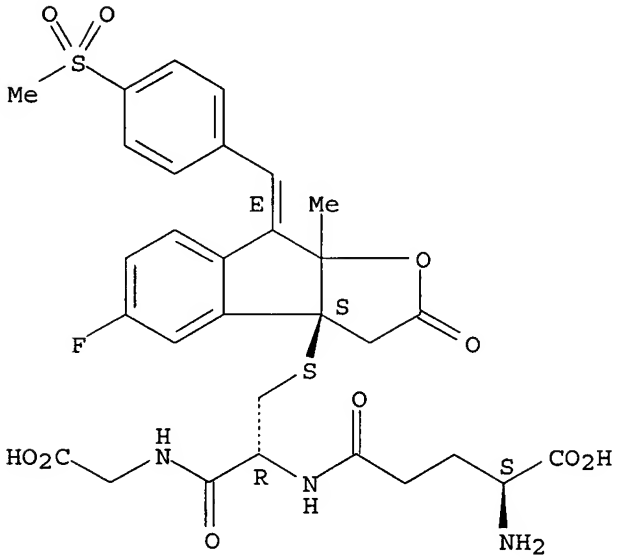
RN 266689-09-2 USPATFULL
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



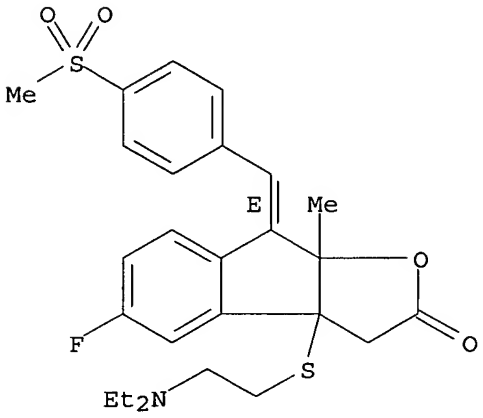
RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L90 ANSWER 21 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2003:165528 USPATFULL
TITLE: Method for treating a patient with neoplasia by treatment with a platinum coordination complex
INVENTOR(S): Pamukcu, Rifat, Spring House, PA, UNITED STATES
Menander, Kerstin B., Meadowbrook, PA, UNITED STATES

NUMBER	KIND	DATE

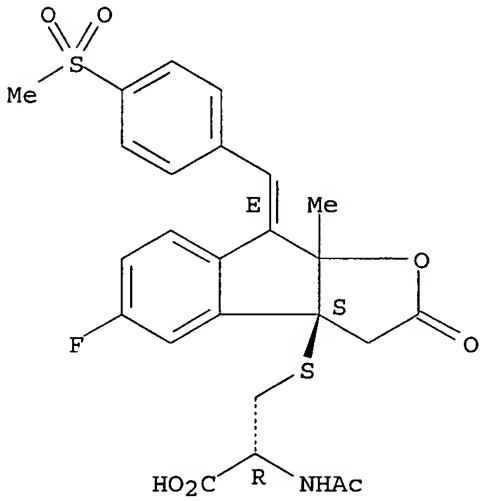
PATENT INFORMATION: US 2003113382 A1 20030619 <--
US 6869944 B2 20050322
APPLICATION INFO.: US 2002-228700 A1 20020827 (10) <--
RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-39154, filed on 3 Jan 2002, ABANDONED Division of Ser. No. US 2001-777395, filed on 6 Feb 2001, GRANTED, Pat. No. US 6359002 Continuation of Ser. No. US 1998-190830, filed on 12 Nov 1998, GRANTED, Pat. No. US 6235782
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Cell Pathways, Inc., 702 Electronic Drive, Horsham, PA, 19044
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Page(s)
LINE COUNT: 1108
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a method for treating a patient with neoplasia by an adjuvant therapy that includes treatment with an antineoplastic platinum coordination complex.

IT **266689-09-2 266689-11-6 268545-30-8**
(paclitaxel derivative and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)

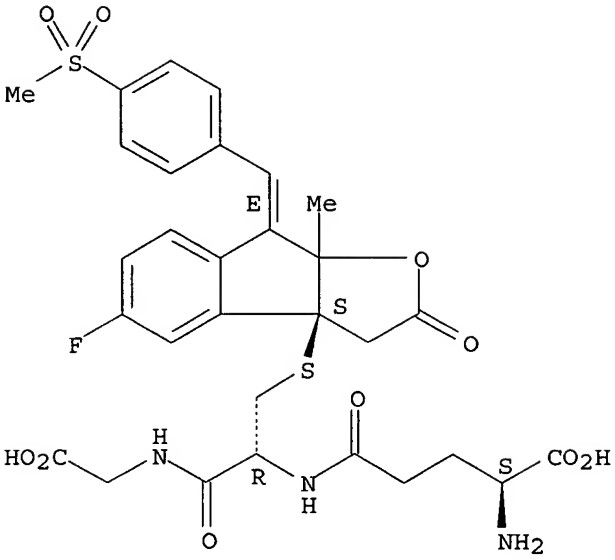
RN 266689-09-2 USPATFULL
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



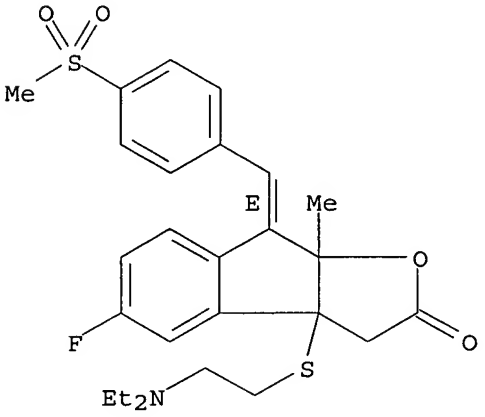
RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L90 ANSWER 22 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2003:159803 USPATFULL
TITLE: Methods for identifying compounds for inhibition of neoplastic lesions, and pharmaceutical compositions containing such compounds
INVENTOR(S): Thompson, W. Joseph, Doylestown, PA, UNITED STATES
Liu, Li, Ambler, PA, UNITED STATES
Li, Han, Yardley, PA, UNITED STATES

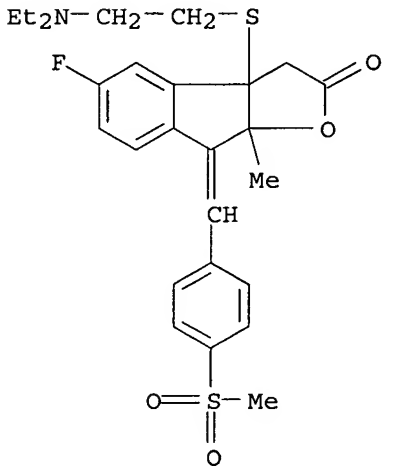
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003109418	A1	20030612	<--

APPLICATION INFO.: US 2002-187762 A1 20020702 (10) <--
RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-414628, filed on 8 Oct 1999, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Cell Pathways, Inc., 702 Electronic Avenue, Horsham, PA, 19044
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 2466
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides pharmaceutical compositions containing compounds for the treatment of neoplasia in mammals. The increase in PKG activity of a compound is determined along with COX inhibitory activity. Growth inhibitory and apoptosis inducing effects on cultured tumor cells are also determined. Compounds that exhibit increase PKG activity, growth inhibition and apoptosis induction, but preferably not substantial prostaglandin inhibitory activity, are desirable for the treatment of neoplasia.

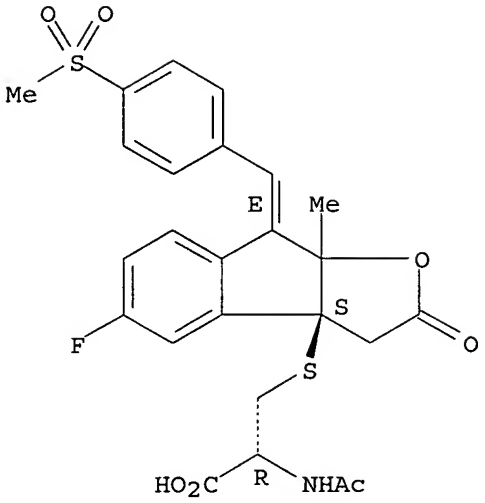
IT **178152-14-2 266689-09-2 266689-11-6**
(cyclooxygenase inhibition- and phosphodiesterase inhibition-based methods for identifying antineoplastic compds., and pharmaceutical compns.)

RN 178152-14-2 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]- (9CI) (CA INDEX NAME)



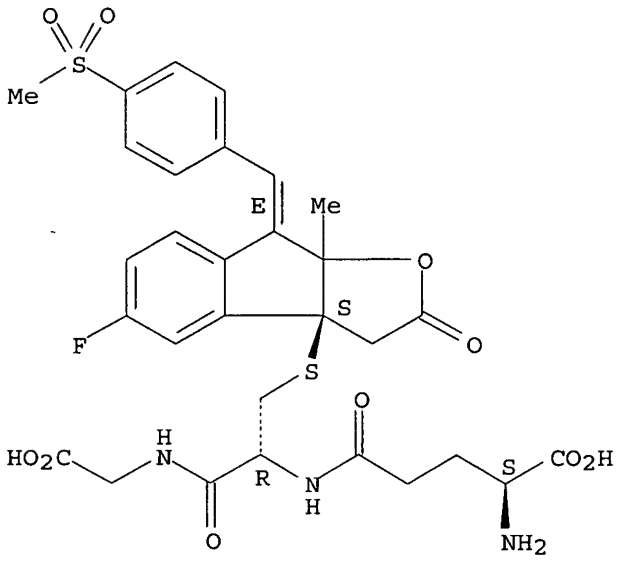
RN 266689-09-2 USPATFULL
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L90 ANSWER 23 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2003:115838 USPATFULL
TITLE: Method for treating a patient with neoplasia by treatment with a vinca alkaloid derivative
INVENTOR(S): Pamukcu, Rifat, Spring House, PA, United States
Lobacki, Joseph M., North Wales, PA, United States
PATENT ASSIGNEE(S): Cell Pathways, Inc., Horsham, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 6555547	B1	20030429		<--
APPLICATION INFO.:	US 2000-515714		20000228	(9)	<--

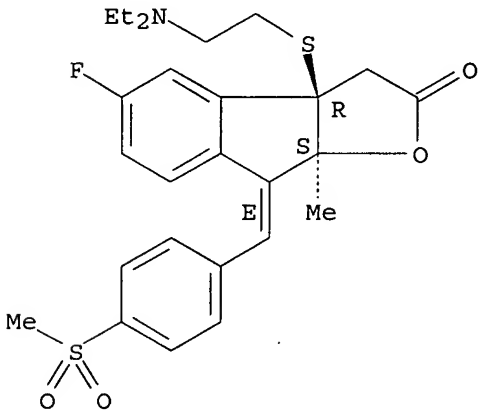
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Jones, Dwayne C.
LEGAL REPRESENTATIVE: Stevenson, Robert W.
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 41 Drawing Figure(s); 29 Drawing Page(s)
LINE COUNT: 2838
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a method for treating a patient with neoplasia by an adjuvant therapy that includes treatment with an antineoplastic vinca alkaloid derivative.

IT **177982-86-4 177983-07-2 177983-08-3**
(method for treating a patient with neoplasia by treatment with a vinca alkaloid derivative in combination with a cGMP phosphodiesterase inhibitor in relation to cyclooxygenase and protein kinase G and β-catenins)

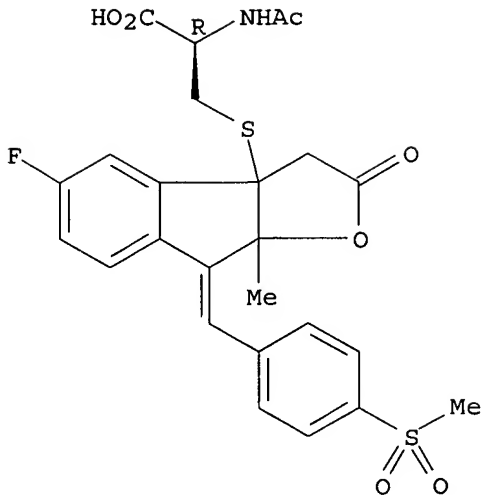
RN 177982-86-4 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (3aR,8E,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



RN 177983-07-2 USPATFULL
CN L-Cysteine, N-acetyl-S-[5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

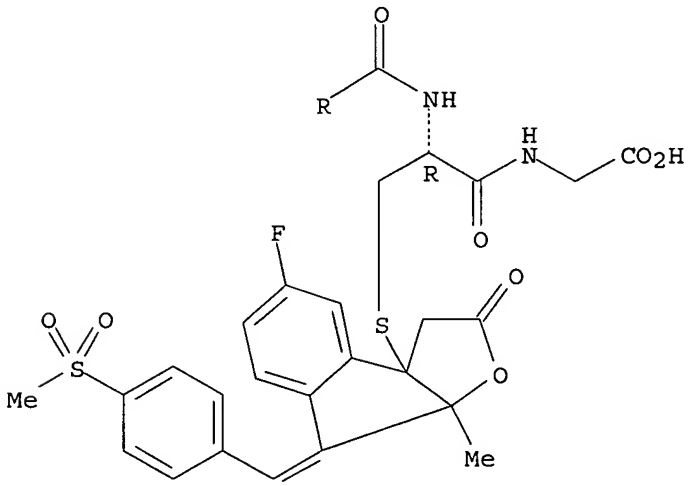
Absolute stereochemistry.
Double bond geometry unknown.



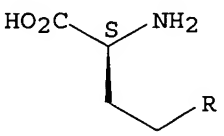
RN 177983-08-3 USPATFULL
CN Glycine, L-γ-glutamyl-S-[5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



PAGE 2-A



L90 ANSWER 24 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2002:337921 USPATFULL			
TITLE:	Method for treating a patient with neoplasia by treatment with a gonadotropin releasing hormone analog			
INVENTOR(S):	Pamukcu, Rifat, Spring House, PA, UNITED STATES Menander, Kerstin B., Meadowbrook, PA, UNITED STATES Alila, Hector, North Wales, PA, UNITED STATES			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002193286	A1	20021219	<--
APPLICATION INFO.:	US 2002-136140	A1	20020430 (10)	<--
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2001-968207, filed on 2 Oct 2001, ABANDONED Continuation of Ser. No. US 2000-718113, filed on 20 Nov 2000, ABANDONED Continuation of Ser. No. US 1998-190030, filed on 12 Nov 1998, ABANDONED			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	Cell Pathways, Inc., 702 Electronic Drive, Horsham, PA, 19044			
NUMBER OF CLAIMS:	10			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	13 Drawing Page(s)			
LINE COUNT:	1052			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

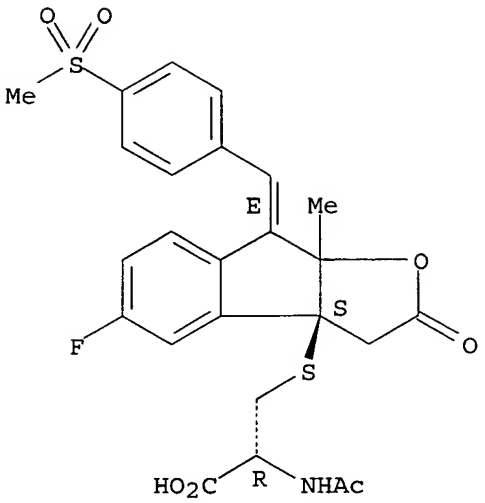
AB This invention provides a method or treating a patient with neoplasia by an adjuvant therapy that includes treatment with a gonadotropin-releasing hormone analog.

IT **266689-09-2 266689-11-6 268545-30-8**
(gonadotropin releasing hormone analog and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)

RN 266689-09-2 USPATFULL

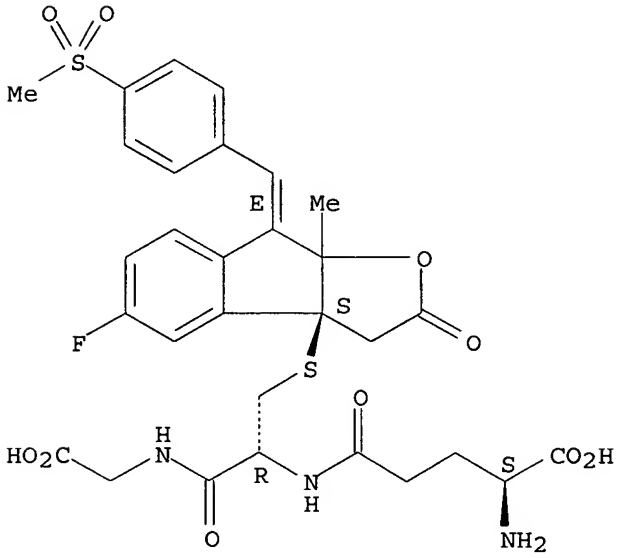
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



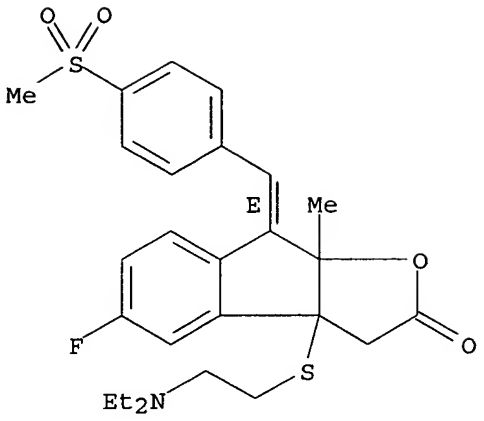
RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L90 ANSWER 25 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2002:251769 USPATFULL			
TITLE:	Method for treating a patient with neoplasia by treatment with a paclitaxel derivative			
INVENTOR(S):	Pamukcu, Rifat, Spring House, PA, UNITED STATES Menander, Kerstin B., Meadowbrook, PA, UNITED STATES			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002137722	A1	20020926	<--
	US 6472420	B2	20021029	
APPLICATION INFO.:	US 2002-38634	A1	20020103 (10)	<--
RELATED APPLN. INFO.:	Division of Ser. No. US 2001-777359, filed on 6 Feb 2001, GRANTED, Pat. No. US 6365627 Continuation of Ser. No. US 1998-190830, filed on 12 Nov 1998, GRANTED, Pat. No. US 6235782			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	Cell Pathways, Inc., 702 Electronic Drive, Horsham, PA, 19044			
NUMBER OF CLAIMS:	3			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	15 Drawing Page(s)			
LINE COUNT:	1073			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

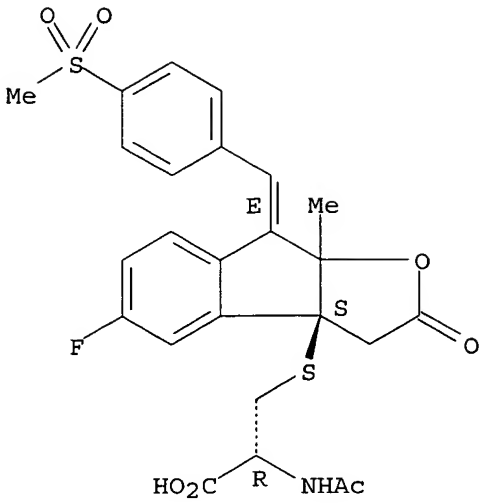
AB This invention provides a method for treating a patient with neoplasia by an adjuvant therapy that includes treatment with a paclitaxel derivative.

IT **266689-09-2 266689-11-6 268545-30-8**
(paclitaxel derivative and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)

RN 266689-09-2 USPATFULL

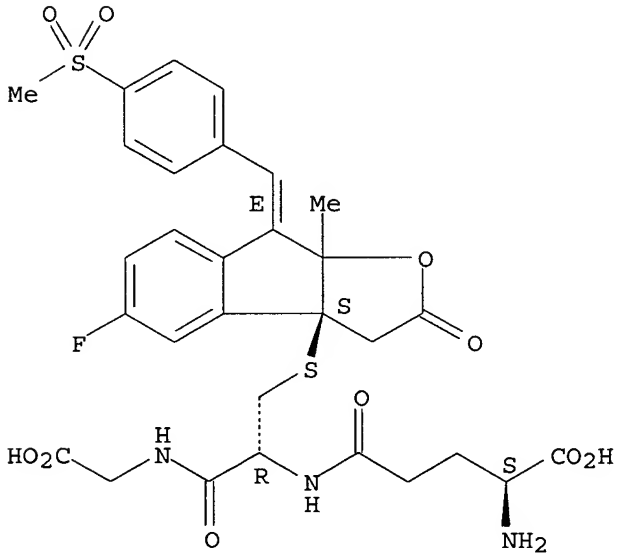
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



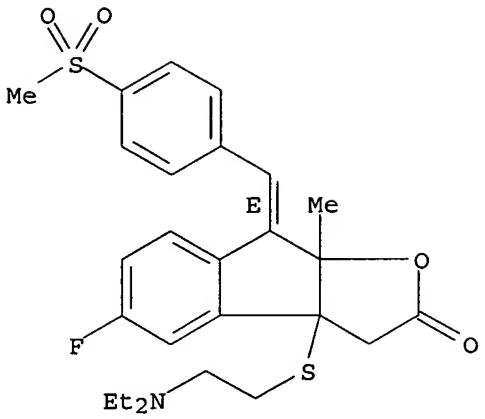
RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

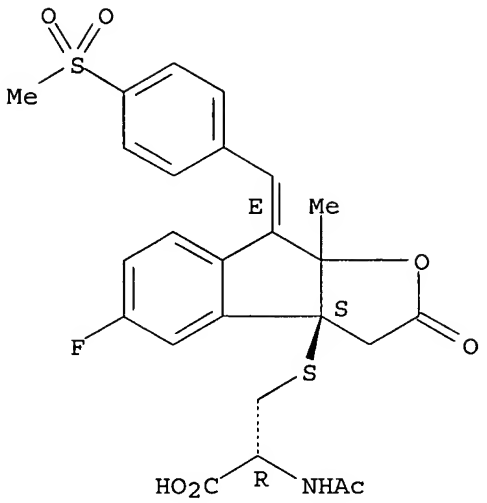


L90 ANSWER 26 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2002:172398 USPATFULL
TITLE: Method for treating a patient with neoplasla by treatment with a platinum coordination complex
INVENTOR(S): Pamukcu, Rifat, Spring House, PA, UNITED STATES
Menander, Kerstin B., Meadowbrook, PA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002091157	A1	20020711	<--
APPLICATION INFO.:	US 2002-39154	A1	20020103 (10)	<--

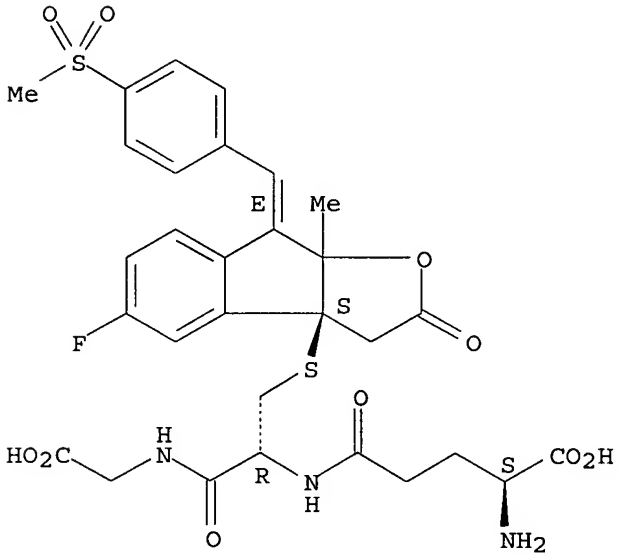
RELATED APPLN. INFO.: Division of Ser. No. US 2001-777395, filed on 6 Feb 2001, PATENTED Continuation of Ser. No. US 1998-190830, filed on 12 Nov 1998, PATENTED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Cell Pathways, Inc., 702 Electronic Drive, Horsham, PA, 19044
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Page(s)
LINE COUNT: 1110
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a method for treating a patient with neoplasia by an adjuvant therapy that includes treatment with an antineoplastic platinum coordination complex.
IT **266689-09-2 266689-11-6 268545-30-8**
(paclitaxel derivative and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)
RN 266689-09-2 USPATFULL
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



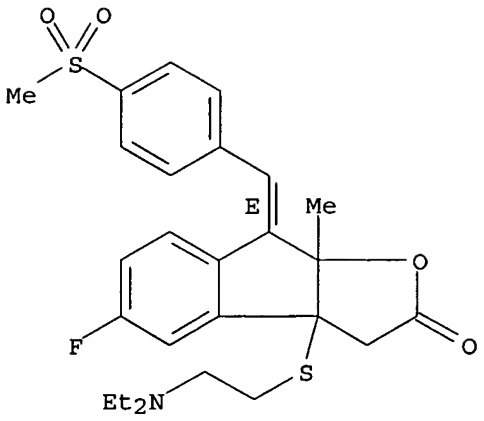
RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L90 ANSWER 27 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2002:37866 USPATFULL			
TITLE:	Method for treating a patient with neoplasia by treatment with a pyrimidine analog			
INVENTOR(S):	Pamukcu, Rifat, Spring House, PA, UNITED STATES Menander, Kerstin B., Meadowbrook, PA, UNITED STATES			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002022586	A1	20020221	<--
APPLICATION INFO.:	US 2000-734633	A1	20001212 (9)	<--
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1998-190343, filed on 12 Nov 1998, ABANDONED			
	NUMBER	DATE		
PRIORITY INFORMATION:	WO 2000-WO27403	20000518		<--
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	Robert W. Stevenson, Cell Pathways, Inc., 702 Electronic Drive, Horsham, PA, 19044			
NUMBER OF CLAIMS:	10			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	13 Drawing Page(s)			
LINE COUNT:	1084			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

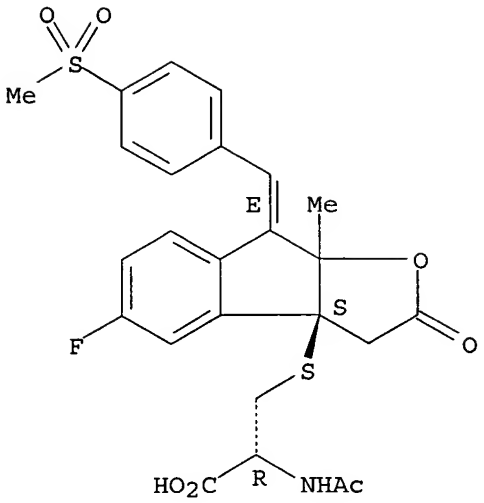
AB This invention provides a method for treating a patient with neoplasia by an adjuvant therapy that includes treatment with a pyrimidine analog.

IT **266689-09-2 266689-11-6 268545-30-8**
(pyrimidine analog and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)

RN 266689-09-2 USPATFULL

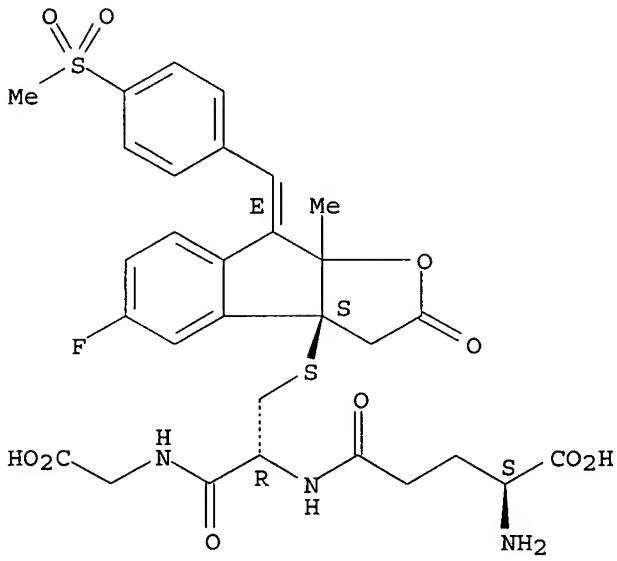
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



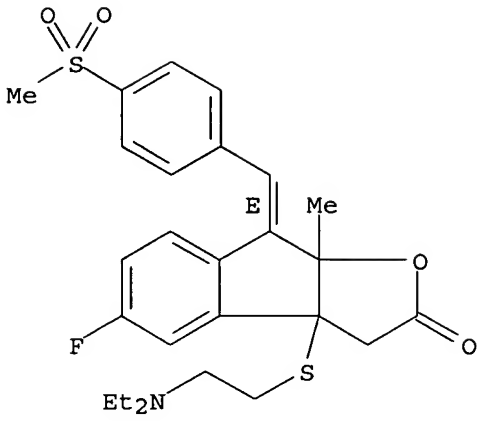
RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L90 ANSWER 28 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2002:16884 USPATFULL				
TITLE:	METHODS FOR IDENTIFYING COMPOUNDS FOR INHIBITION OF NEOPLASTIC LESIONS, AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS				
INVENTOR(S):	THOMPSON, W. JOSEPH, DOYLESTOWN, PA, UNITED STATES LIU, LI, AMBLER, PA, UNITED STATES LI, HAN, YARDLEY, PA, UNITED STATES				
	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 2002009764	A1	20020124		<--
APPLICATION INFO.:	US 1999-414628	A1	19991008	(9)	<--
DOCUMENT TYPE:	Utility				
FILE SEGMENT:	APPLICATION				
LEGAL REPRESENTATIVE:	ROBERT W STEVENSON, CELL PATHWAYS INC, 702 ELECTRONIC DR, HORSHAM, PA, 10944				
NUMBER OF CLAIMS:	12				
EXEMPLARY CLAIM:	1				
NUMBER OF DRAWINGS:	25 Drawing Page(s)				
LINE COUNT:	2468				

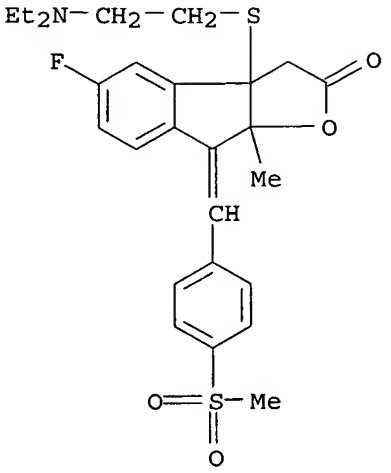
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides pharmaceutical compositions containing compounds for the treatment of neoplasia in mammals. The increase in PKG activity of a compound is determined along with COX inhibitory activity. Growth inhibitory and apoptosis inducing effects on cultured tumor cells are also determined. Compounds that exhibit increase PKG activity, growth inhibition and apoptosis induction, but preferably not substantial prostaglandin inhibitory activity, are desirable for the treatment of neoplasia.

IT **178152-14-2 266689-09-2 266689-11-6**
(cyclooxygenase inhibition- and phosphodiesterase inhibition-based methods for identifying antineoplastic compds., and pharmaceutical compns.)

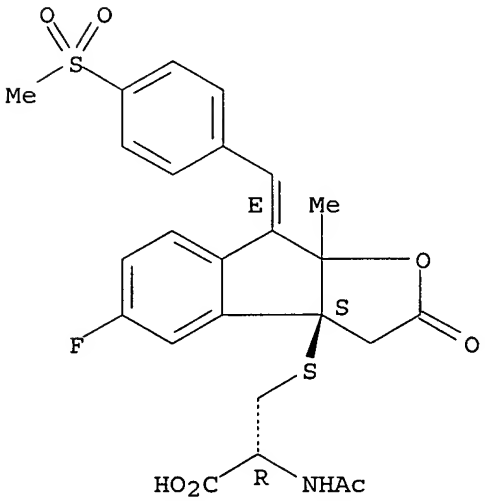
RN 178152-14-2 USPATFULL

CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-(9CI) (CA INDEX NAME)



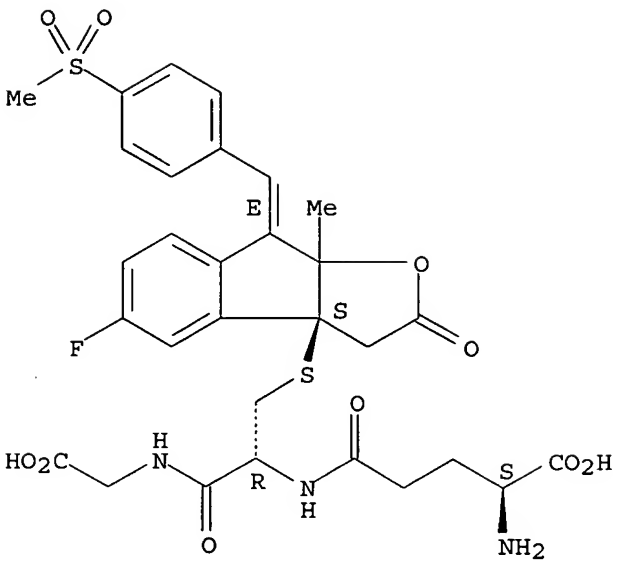
RN 266689-09-2 USPATFULL
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L90 ANSWER 29 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2001:155786 USPATFULL			
TITLE:	Method for treating a patient with neoplasia by treatment with a paclitaxel derivative			
INVENTOR(S):	Pamukcu, Rifat, Spring House, PA, United States Menander, Kerstin B., Meadowbrook, PA, United States			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2001021720	A1	20010913	<--
	US 6365627	B2	20020402	
APPLICATION INFO.:	US 2001-777359	A1	20010206 (9)	<--
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1998-190637, filed on 12 Nov 1998, GRANTED, Pat. No. US 6235776			
	NUMBER	DATE		
PRIORITY INFORMATION:	JP 2000-46834	20000218		<--
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	Robert W. Stevenson - 31064, Cell Pathways, Inc., 702 Electronic Drive, Horsham, PA, 19044			
NUMBER OF CLAIMS:	1			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	15 Drawing Page(s)			
LINE COUNT:	1061			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a method for treating a patient with neoplasia by an adjuvant therapy that includes treatment with a paclitaxel derivative.

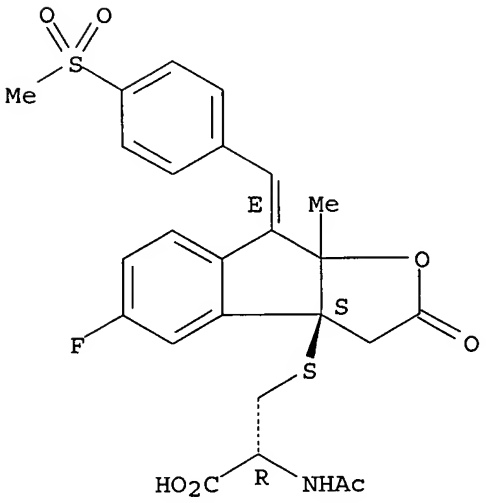
IT **266689-09-2 266689-11-6 268545-30-8**
(paclitaxel derivative and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)

RN 266689-09-2 USPATFULL

CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-

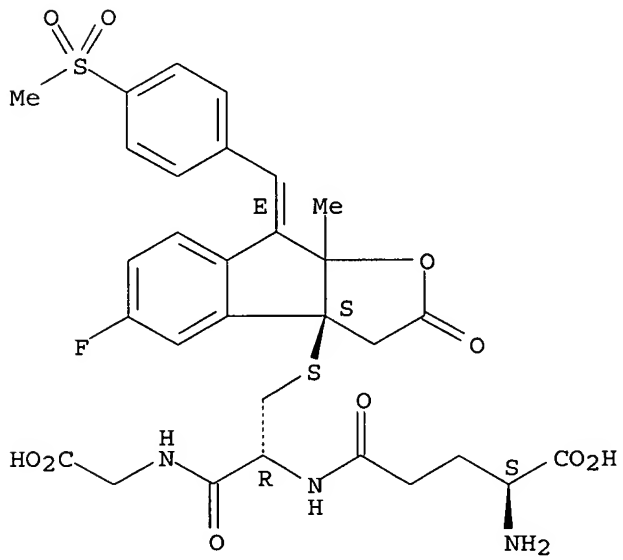
yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



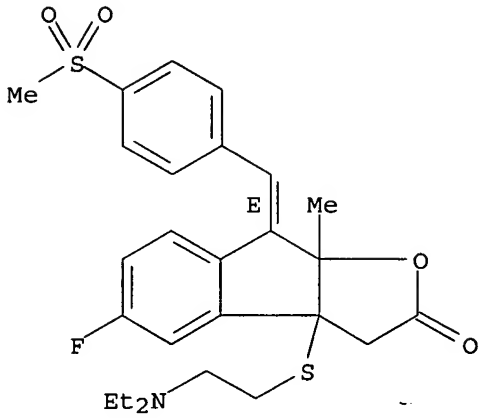
RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

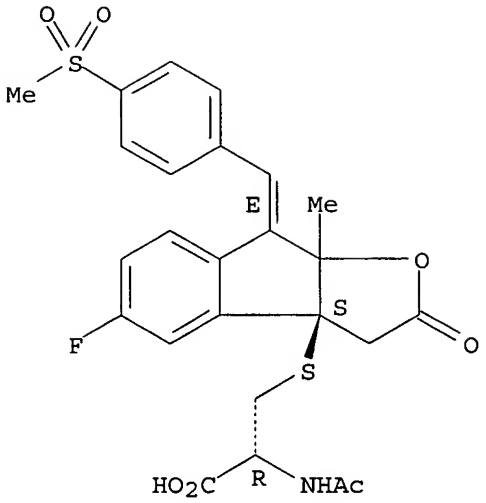


L90 ANSWER 30 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2001:128870 USPATFULL
TITLE: Method for treating a patient with neoplasia by treatment with a platinum coordination complex
INVENTOR(S): Pamukcu, Rifat, Spring House, PA, United States
Menander, Kerstin B., Meadowbrook, PA, United States

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2001012858	A1	20010809	<--
	US 6359002	B2	20020319	
APPLICATION INFO.:	US 2001-777395	A1	20010206 (9)	<--

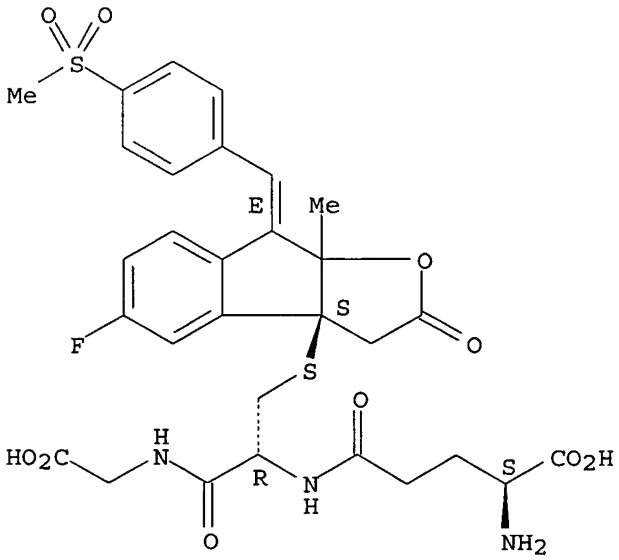
RELATED APPLN. INFO.: Continuation of Ser. No. US 1998-190830, filed on 12 Nov 1998, GRANTED, Pat. No. US 6235782
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Cell Pathways, Inc., 702 Electronic Drive, Horsham, PA, 19044
NUMBER OF CLAIMS: 1
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Page(s)
LINE COUNT: 1097
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a method for treating a patient with neoplasia by an adjuvant therapy that includes treatment with an antineoplastic platinum coordination complex.
IT **266689-09-2 266689-11-6 268545-30-8**
(paclitaxel derivative and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)
RN 266689-09-2 USPATFULL
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



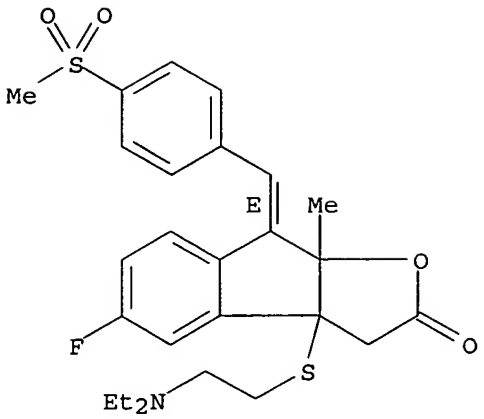
RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

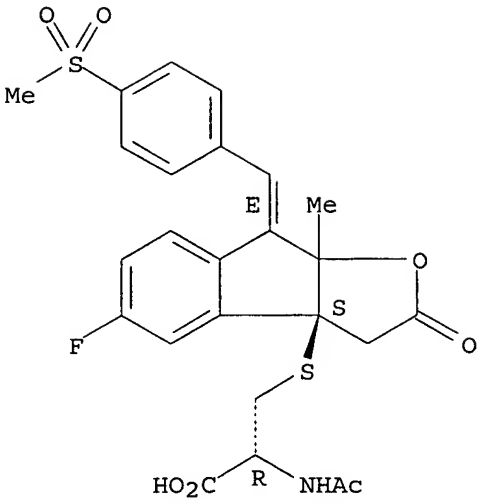


L90 ANSWER 31 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2001:75434 USPATFULL
TITLE: Method for treating a patient with neoplasia by treatment with a platinum coordination complex
INVENTOR(S): Pamukcu, Rifat, 2 Pump House Dr., Spring House, PA, United States 19477
Menander, Kerstin B., 1420 Stockton Rd., Meadowbrook, PA, United States 19046

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6235782	B1	20010522	<--
APPLICATION INFO.:	US 1998-190830		19981112 (9)	<--

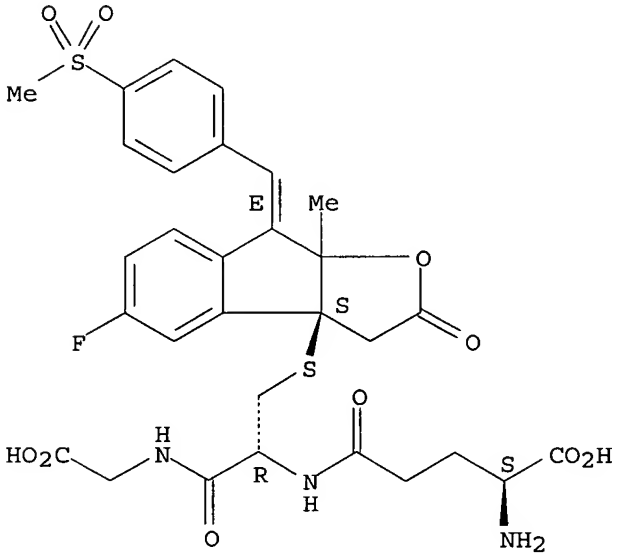
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Jones, Dwayne C.
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Figure(s); 15 Drawing Page(s)
LINE COUNT: 1434
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a method for treating a patient with neoplasia by an adjuvant therapy that includes treatment with an antineoplastic platinum coordination complex.
IT **266689-09-2 266689-11-6 268545-30-8**
(paclitaxel derivative and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)
RN 266689-09-2 USPATFULL
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



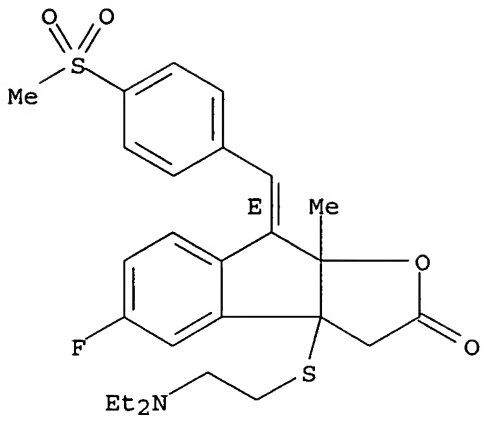
RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L90 ANSWER 32 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2001:75428 USPATFULL				
TITLE:	Method for treating a patient with neoplasia by treatment with a paclitaxel derivative				
INVENTOR(S):	Pamukcu, Rifat, Spring House, PA, United States Menander, Kerstin B., Meadowbrook, PA, United States				
PATENT ASSIGNEE(S):	Cell Pathways, Inc., Horsham, PA, United States (U.S. corporation)				
	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 6235776	B1	20010522		<--
APPLICATION INFO.:	US 1998-190637		19981112	(9)	<--
DOCUMENT TYPE:	Utility				
FILE SEGMENT:	Granted				
PRIMARY EXAMINER:	Jones, Dwayne C.				
LEGAL REPRESENTATIVE:	Stevenson, Robert W.				
NUMBER OF CLAIMS:	10				
EXEMPLARY CLAIM:	1				
NUMBER OF DRAWINGS:	24 Drawing Figure(s); 15 Drawing Page(s)				
LINE COUNT:	1396				

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

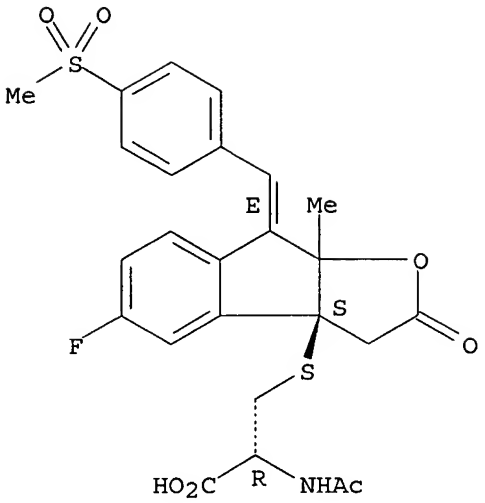
AB This invention provides a method for treating a patient with neoplasia by an adjuvant therapy that includes treatment with a paclitaxel derivative.

IT **266689-09-2 266689-11-6 268545-30-8**
(paclitaxel derivative and cGMP-specific phosphodiesterase inhibitor for treatment of neoplasia)

RN 266689-09-2 USPATFULL

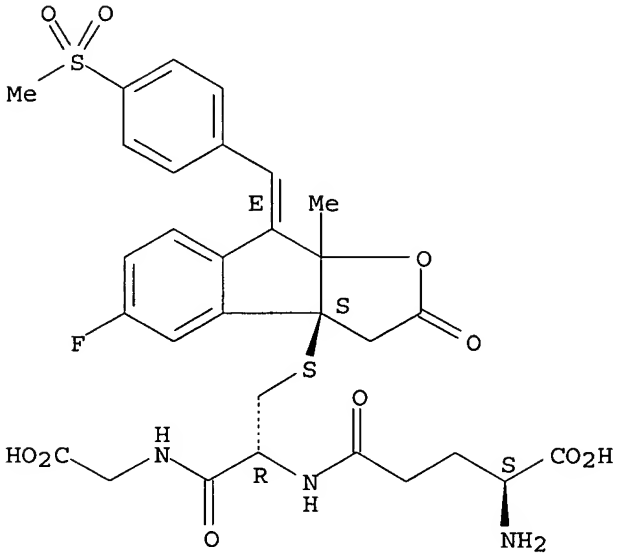
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



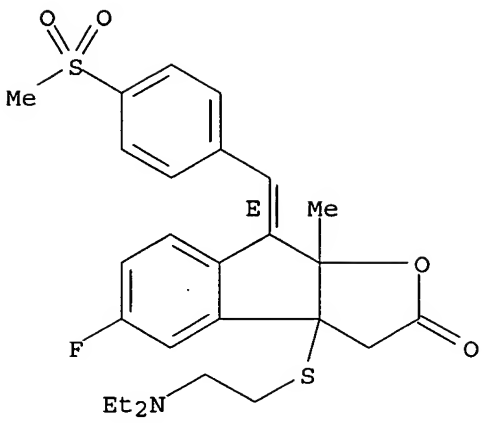
RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 268545-30-8 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (8E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L90 ANSWER 33 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2001:36620 USPATFULL
TITLE:	Method of using a novel phosphodiesterase in pharmaceutical screeing to identify compounds for treatment of neoplasia
INVENTOR(S):	Liu, Li, Northwales, PA, United States Pamukcu, Rifat, Spring House, PA, United States Thompson, W. Joseph, Doylestown, PA, United States Piazza, Gary A., Doylestown, PA, United States Li, Han, Yardley, PA, United States Zhu, Bing, Mobile, AL, United States
PATENT ASSIGNEE(S):	Cell Pathways, Inc., Hosham, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 6200771	B1	20010313		<--
APPLICATION INFO.:	US 1998-173375		19981015	(9)	<--
DOCUMENT TYPE:	Utility				
FILE SEGMENT:	Granted				
PRIMARY EXAMINER:	Gitomer, Ralph				
LEGAL REPRESENTATIVE:	Stevenson, Robert W.				
NUMBER OF CLAIMS:	13				
EXEMPLARY CLAIM:	1				
NUMBER OF DRAWINGS:	21 Drawing Figure(s); 15 Drawing Page(s)				
LINE COUNT:	1383				

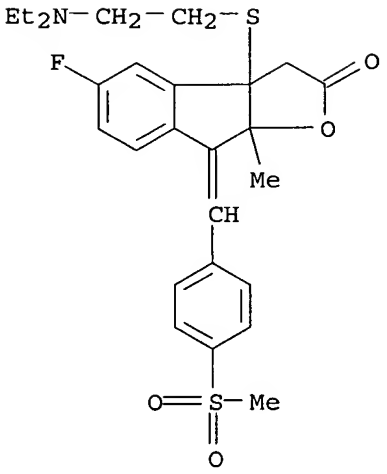
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for identifying compounds useful for the treatment of neoplasia involves acertaining whether such compounds exhibit an ability to inhibit a PDE that is characterized by cGMP specificity, cooperative kinetic behavior and insensitivity to phosphorylation.

IT **178152-14-2 266689-09-2 266689-11-6**
(cyclooxygenase inhibition- and phosphodiesterase inhibition-based methods for identifying antineoplastic compds., and pharmaceutical compns.)

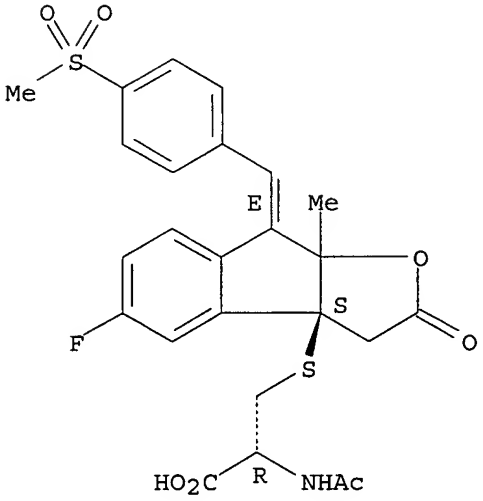
RN 178152-14-2 USPATFULL

CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-(9CI) (CA INDEX NAME)



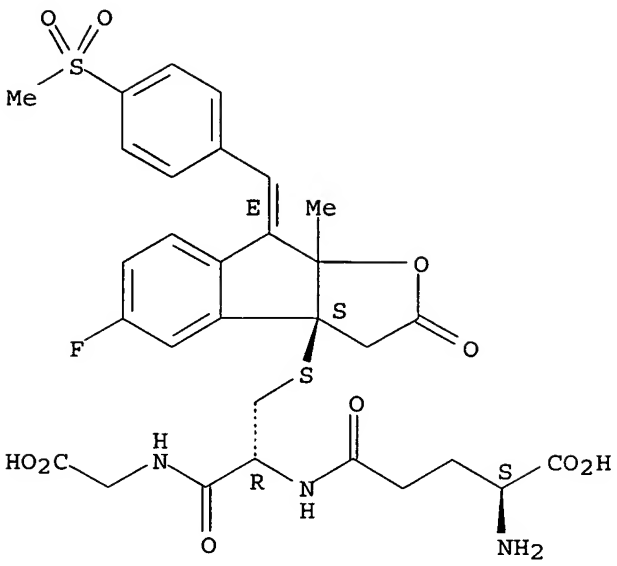
RN 266689-09-2 USPATFULL
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L90 ANSWER 34 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2000:134720 USPATFULL
TITLE:	Method for selecting compounds for inhibition of neoplastic lesions
INVENTOR(S):	Thompson, W. Joseph, Doylestown, PA, United States Liu, Li, Ambler, PA, United States Li, Han, Yardley, PA, United States
PATENT ASSIGNEE(S):	Cell Pathways, Inc., Horsham, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6130053		20001010	<--
APPLICATION INFO.:	US 1999-366003		19990803 (9)	<--

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Gitomer, Ralph
LEGAL REPRESENTATIVE:	Stevenson, Robert W.
NUMBER OF CLAIMS:	12
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	19 Drawing Figure(s); 17 Drawing Page(s)
LINE COUNT:	2220

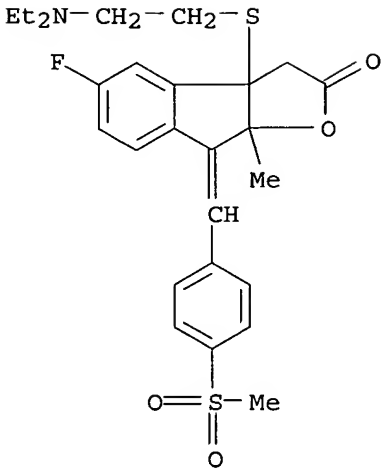
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for selecting compounds for the treatment of neoplasia includes assessing whether the compounds cause an increase in PKG activity in the neoplasia of interest.

IT **178152-14-2 266689-09-2 266689-11-6**
(cyclooxygenase inhibition- and phosphodiesterase inhibition-based methods for identifying antineoplastic compds., and pharmaceutical compns.)

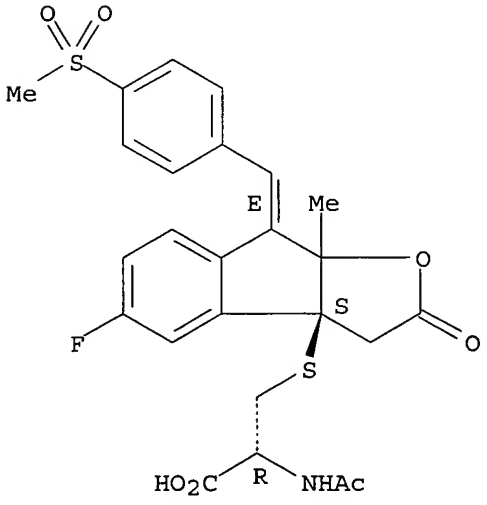
RN 178152-14-2 USPATFULL

CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-(9CI) (CA INDEX NAME)



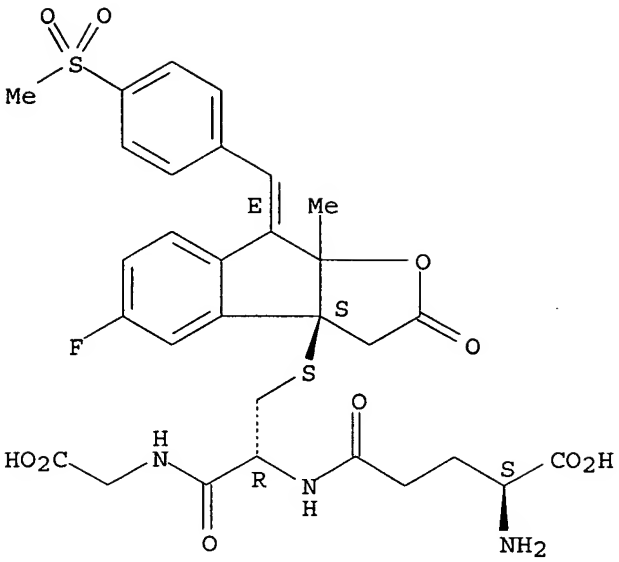
RN 266689-09-2 USPATFULL
CN L-Cysteine, N-acetyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 266689-11-6 USPATFULL
CN Glycine, L-γ-glutamyl-S-[(3aS,8E)-5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L90 ANSWER 35 OF 40 USPATFULL on STN

ACCESSION NUMBER:	97:115317 USPATFULL
TITLE:	Lactone compounds for treating patients with precancerous lesions
INVENTOR(S):	Gross, Paul, Stockton, CA, United States Sperl, Gerhard, Stockton, CA, United States Pamukcu, Rifat, Spring House, PA, United States Brendel, Klaus, Tucson, AZ, United States
PATENT ASSIGNEE(S):	Cell Pathways, Inc., Denver, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 5696159		19971209		<--
APPLICATION INFO.:	US 1994-265396		19940803	(8)	<--
DOCUMENT TYPE:	Utility				
FILE SEGMENT:	Granted				
PRIMARY EXAMINER:	Owens, Amelia				
LEGAL REPRESENTATIVE:	Brinks Hofer Gilson & Lione				
NUMBER OF CLAIMS:	18				
EXEMPLARY CLAIM:	1				
LINE COUNT:	1540				

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

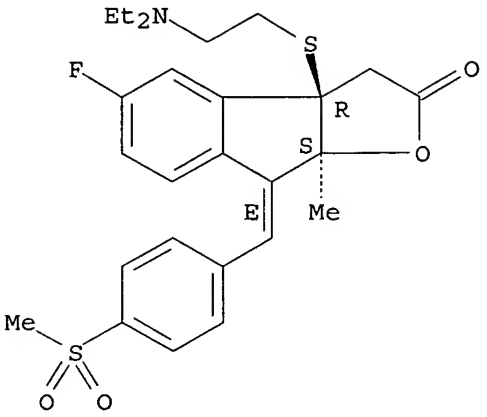
AB Substituted lactone compounds are useful in the treatment of precancerous lesions.

IT **177982-86-4P 177983-06-1P 177983-07-2P**
177983-08-3P 178152-14-2P
(preparation of oxotetrahydrofuran lactone antitumor agents)

RN 177982-86-4 USPATFULL

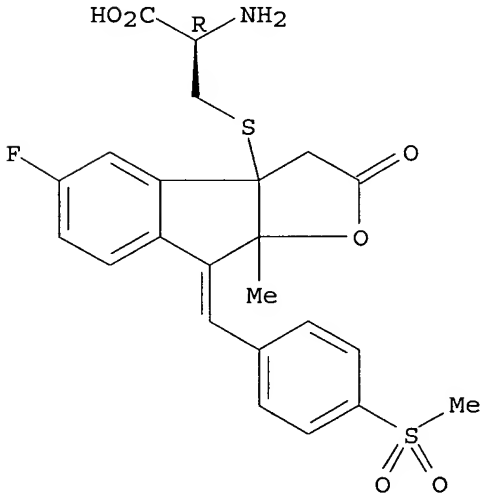
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-, (3aR,8E,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



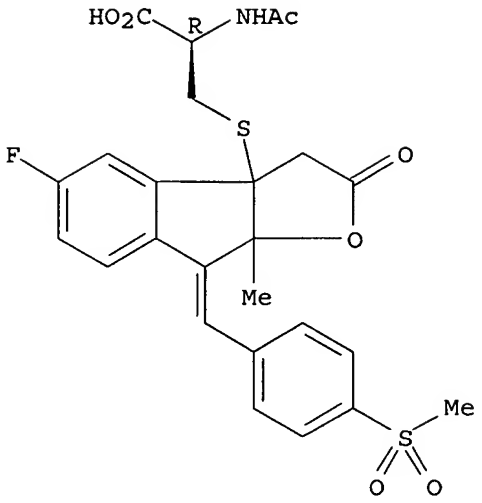
RN 177983-06-1 USPATFULL
CN L-Cysteine, S-[5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 177983-07-2 USPATFULL
CN L-Cysteine, N-acetyl-S-[5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-(9CI) (CA INDEX NAME)

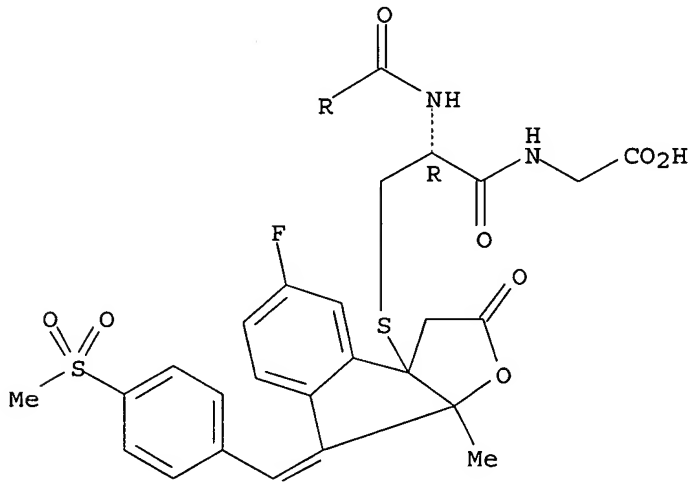
Absolute stereochemistry.
Double bond geometry unknown.



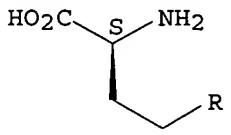
RN 177983-08-3 USPATFULL
CN Glycine, L-γ-glutamyl-S-[5-fluoro-2,3,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]-2-oxo-3aH-indeno[2,1-b]furan-3a-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

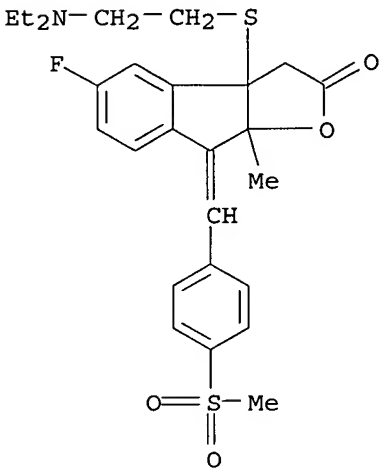
PAGE 1-A



PAGE 2-A



RN 178152-14-2 USPATFULL
CN 2H-Indeno[2,1-b]furan-2-one, 3a-[[2-(diethylamino)ethyl]thio]-5-fluoro-3,3a,8,8a-tetrahydro-8a-methyl-8-[[4-(methylsulfonyl)phenyl]methylene]- (9CI) (CA INDEX NAME)



=> d ibib ed ab hitind 36-37
YOU HAVE REQUESTED DATA FROM FILE 'CHEMINFORMRX, WPIX, HCAPLUS, USPATFULL, TOXCENTER, IFICDB' - CONTINUE? (Y)/N:y

L90 ANSWER 36 OF 40 TOXCENTER COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:170979 TOXCENTER
COPYRIGHT: Copyright 2006 ACS
DOCUMENT NUMBER: CA12505058302R
TITLE: Preparation of oxotetrahydrofuran lactone antitumor agents
AUTHOR(S): Gross, Paul; Sperl, Gerhard; Pamukcu, Rifat; Brendel, Klaus
CORPORATE SOURCE: ASSIGNEE: University of Arizona
PATENT INFORMATION: WO 963987 A1 15 Feb 1996
SOURCE: (**1996**) PCT Int. Appl., 61 pp.
CODEN: PIXXD2.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Patent
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1996:379711
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20020730
ED Entered STN: 20011116
Last Updated on STN: 20020730
AB The title compds. [I; R1, R2 = H, amino, alkyl, alkoxy, azido, OH, halogen, acetoxyl, benzoxy, (un)substituted Ph; R3 = H, halogen, azido, alkyl, alkoxy, CN, OH, PhS, etc.; R4 = H, OH, halogen, alkyl, alkoxy, dialkylamino; R5 = H, OH, halogen, alkyl, alkoxy, dialkylamino, NH2; R6 = H, alkyl, HO, alkoxy, halogen, R7 = H, (un)substituted alkyl, Ph, etc.; R8, R9 = H, alkyl, HO, alkoxy, halogen; R10, R11 = H, haloge, alkoxy,

alkyl; R12 = H, halogen, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, etc.; X = C, N (when X = N then R6 is absent)], useful in the treatment of precancerous lesions and neoplasms, are prepared Thus, (Z)-5-fluoro-2-methyl-1-(p-methylsulfinylbenzylidene)-3-indenylacetic acid was brominated with N-bromosuccinimide, producing racemic threo-(E)-1-bromo-1-(butan-1',4'-olido)-[3',4':1,2]-6-fluoro-2-methyl-3-(p-methylsulfinylbenzylidene)indane, m.p. 162°, which demonstrated a IC50 of 0.081 uM against the HT-29p136 human melanoma adenocarcinoma cell line.

CC 27-6

ST Miscellaneous Descriptors
oxotetrahydrofuran prepn antitumor agent; anticancer agent prepn oxotetrahydrofuran; colon cancer treatment prepn oxotetrahydrofuran

RN 52-90-4 (L-Cysteine)
70-18-8 (Glutathione)
86-81-7 (3,4,5-Trimethoxybenzaldehyde)
96-32-2 (Methyl bromoacetate)
100-52-7 (Benzaldehyde)
104-87-0 (4-Methylbenzaldehyde)
104-88-1 (4-Chlorobenzaldehyde)
123-62-6 (Propanoic anhydride)
137-40-6 (Sodium propionate)
321-28-8 (2-Fluoroanisole)
372-09-8 (Cyanoacetic acid)
459-57-4 (Benzaldehyde, 4-fluoro-)
609-08-5 (Diethyl methylmalonate)
616-91-1 (N-Acetyl-L-Cysteine)
824-94-2 (4-Methoxybenzyl chloride)
1942-52-5 (Ethanethiol, 2-(diethylamino)-, hydrochloride)
2882-15-7 (1H-Indole-3-acetic acid, 5-methoxy-2-methyl-)
2927-34-6 (Benzene, 1,2-difluoro-4-methyl-)
3446-89-7 (Benzaldehyde, 4-(methylthio)-)
71987-67-2 (1H-Indole-3-acetic acid, 5-fluoro-2-methyl-)
351-54-2 (Benzaldehyde, 3-fluoro-4-methoxy-)
34036-07-2 (Benzaldehyde, 3,4-difluoro-)
363-24-6 (PGE2)

RN 177982-65-9; 177982-66-0; 177982-77-3; 177982-78-4; 177982-79-5; 177982-80-8; 177982-81-9; 177982-82-0; 177982-83-1; 177982-84-2; 177982-85-3; **177982-86-4**; 177982-87-5; 177982-88-6; 177982-89-7; 177982-90-0; 177982-91-1; 177982-92-2; 177982-93-3; 177982-94-4; 177982-95-5; 177982-96-6; 177982-97-7; 177982-98-8; 177982-99-9; 177983-00-5; 177983-01-6; 177983-02-7; 177983-03-8; 177983-04-9; 177983-05-0; **177983-06-1**; **177983-07-2**; **177983-08-3**; 177983-09-4; 177983-10-7; 177983-11-8; 177983-12-9; **178152-14-2**; 178152-15-3; 75-65-0; 32004-66-3; 38194-50-2; 51927-26-5; 177982-67-1; 53-86-1; 1226-02-4; 1601-20-3; 16203-90-0; 16204-04-9; 16204-05-0; 17726-27-1; 22138-72-3; 22138-73-4; 32004-52-7; 32004-55-0; 32004-57-2; 32004-62-9; 32004-64-1; 32004-65-2; 32004-67-4; 32004-68-5; 32004-75-4; 32040-88-3; 33036-54-3; 38226-47-0; 41201-58-5; 50703-56-5; 52102-75-7; 52427-11-9; 59864-04-9; 99046-64-7; 142958-51-8; 142988-13-4; 177982-68-2; 177982-69-3; 177982-70-6; 177982-71-7; 177982-72-8; 177982-73-9; 177982-74-0; 177982-75-1; 177982-76-2

L90 ANSWER 37 OF 40 TOXCENTER COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:162107 TOXCENTER
COPYRIGHT: Copyright 2006 ACS
DOCUMENT NUMBER: CA11517183274C
TITLE: Preparation of (arylalkyl)hydroxythiazoles as 5-lipoxygenase inhibitors
AUTHOR(S): Kerdesky, Francis A. J.; Brooks, Dee W.

CORPORATE SOURCE: ASSIGNEE: Abbott Laboratories
PATENT INFORMATION: WO 918744 A1 27 Jun 1991
SOURCE: (**1991**) PCT Int. Appl., 45 pp.
CODEN: PIXXD2.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Patent
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1991:583274
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20021008
ED Entered STN: 20011116
Last Updated on STN: 20021008
AB Title compds. [I and II; R1 = (cyclo)alkyl, (substituted) (cyclo)alkenyl, aryl, arylalkyl, arylalkenyl, heterocyclyl, heterocyclylalkyl; M = H, pharmaceutically acceptable cation, acyl, silyl, etc.; Z = residue of nonsteroidal antiinflammatory drug] were prepared Thus, naproxen in CH2Cl2 at 5° was treated with (COCl)2 and cat. DMF; the mixture was allowed to warm to 23°, stirred 8 h, cooled to 5°, and treated with aqueous NH3 to give 85% amide, which was treated with Lawesson's reagent to give 33% thioamide. The latter in PhMe/pyridine was treated dropwise with α-chlorophenylacetyl chloride followed by 8 h reflux to give 27% I [R1 = Ph, M = H, Z = 1-(6-methoxy-2-naphthyl)ethyl]. I inhibited 5-lipoxygenase with IC50 = 0.06-0.9 μM.
CC 28-7
ST Miscellaneous Descriptors
arylalkylhydroxythiazole prepn lipoxygenase inhibitor; thiazole arylalkylhydroxy prepn lipoxygenase inhibitor
RN 3900-45-6 (2-Acetyl-6-methoxynaphthalene)
1067-74-9 (Methyl diethylphosphonoacetate)
2227-79-4 (Thiobenzamide)
2912-62-1 (Phenylchloroacetyl chloride)
80619-02-9 (5-Lipoxygenase)
1553-60-2 (Ibufenac)
15687-27-1 (Ibuprofen)
55837-18-8 (Butibufen)
RN 22204-53-1; 56600-69-2; 136691-27-5; 136691-29-7; 136691-28-6; 95093-51-9; 123675-40-1; 136690-82-9; 136690-83-0; 136690-84-1; 136690-85-2; 136690-86-3; 136690-87-4; 136690-88-5; 136690-89-6; 136690-90-9; 136690-91-0; 136690-92-1; 136690-93-2; 136690-94-3; 136690-95-4; 136690-96-5; 136690-97-6; 136690-98-7; 136690-99-8; 136691-00-4; 136691-01-5; 136691-02-6; 136691-03-7; 136691-04-8; 136691-05-9; 136691-06-0; 136691-07-1; 136691-08-2; 136691-09-3; 136691-10-6; 136691-11-7; 136691-12-8; 136691-13-9; 136691-14-0; 136691-15-1; 136691-16-2; 136691-17-3; 136691-18-4; 136691-19-5; 136691-20-8; 136691-21-9; 136691-22-0; 136691-23-1; 136691-24-2; 136691-25-3; **136691-26-4**

=> d ibib ab 38
YOU HAVE REQUESTED DATA FROM FILE 'CHEMINFORMRX, WPIX, HCAPLUS, USPATFULL, TOXCENTER, IFICDB' - CONTINUE? (Y)/N:y

L90 ANSWER 38 OF 40 IFICDB COPYRIGHT 2006 IFI on STN
AN 00785986 IFIPAT;IFIUDB;IFICDB
TITLE: SUBSTITUTED 1-(LOWERALKYL-SULFINYLBENZYLIDENE)-3-INDENYLOXYACETIC ACID AND ESTERS THEREOF; ANTIINFLAMMATORY AGENTS, ANTIPYRETICS, ANALGESICS

INVENTOR(S): FORDICE M; JONES H; SHEN T
PATENT ASSIGNEE(S): MERCK & CO INC (54136)

	NUMBER	PK	DATE
PATENT INFORMATION:	US 3737455	A	19730605
	(CITED IN 017 LATER PATENTS)		
APPLICATION INFORMATION:	US 1971-108631		19710121
EXPIRATION DATE:	5 Jun 1990		
FAMILY INFORMATION:	US 3737455		19730605
	DE 2202728		
	FR 2122587		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	CHEMICAL		
	GRANTED		
OTHER SOURCE:	CA 77:126307		

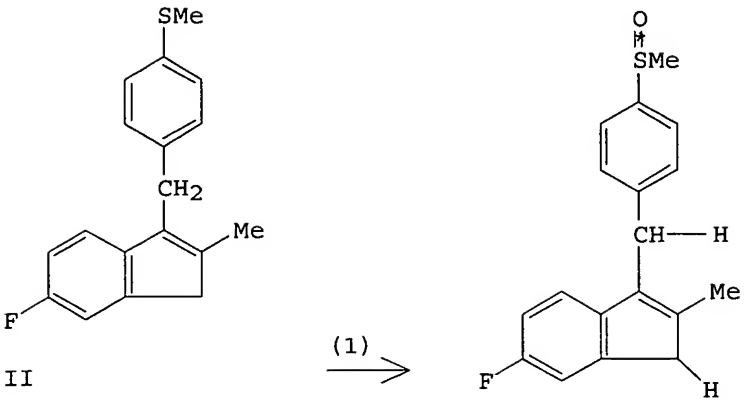
AB NEW SUBSTITUTED INDENE ACIDS AND NON-TOXIC PHARMACEUTICALLY ACCEPTABLE AMIDES, ESTERS AND SALTS DERIVED THEREFROM. THE SUBSTITUTED INDENE ACIDS DISCLOSED HEREIN HAVE ANTI-INFLAMMATORY, ANTI-PYRETIC AND ANALGESIC ACTIVITY. ALSO INCLUDED HEREIN ARE METHODS OF PREPARING SAID INDENE ACID COMPOUNDS, PHARMACEUTICAL COMPOSITIONS HAVING SAID INDENE ACID COMPOUNDS AS AN ACTIVE INGREDIENT AND METHODS OF TREATING INFLAMMATION BY ADMINISTERING THESE PARTICULAR COMPOSITIONS TO PATIENTS.

=> d ibib ab rx 39
YOU HAVE REQUESTED DATA FROM FILE 'CHEMINFORMRX, WPIX, HCAPLUS, USPATFULL, TOXCENTER, IFICDB' - CONTINUE? (Y)/N:y

'IBIB' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid in at least one of the files. Refer to file specific help messages or the STNGUIDE file for information on formats available in individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):bib ab rx

L90 ANSWER 39 OF 40 CHEMINFORMRX COPYRIGHT 2006 FIZ CHEMIE on STN
AN 200117096 CHEMINFORMRX
TI Enantioselective Synthesis of Sulindac.
AU MAGUIRE, A. R.; PAPOT, S.; FORD, A.; TOUHEY, S.; O'CONNOR, R.; CLYNES, M.
CS Dep. Chem., Univ. Coll., Cork, Ire.
SO Synlett(1), 41-44 (2001)
CODEN: SYNLES ISSN: 0936-5214
LA English
AB Both enantiomers (V) are prepared using either (+)- or (-)-DET in the key step. The antipodes are required for a study concerning the metabolism of the title drug.

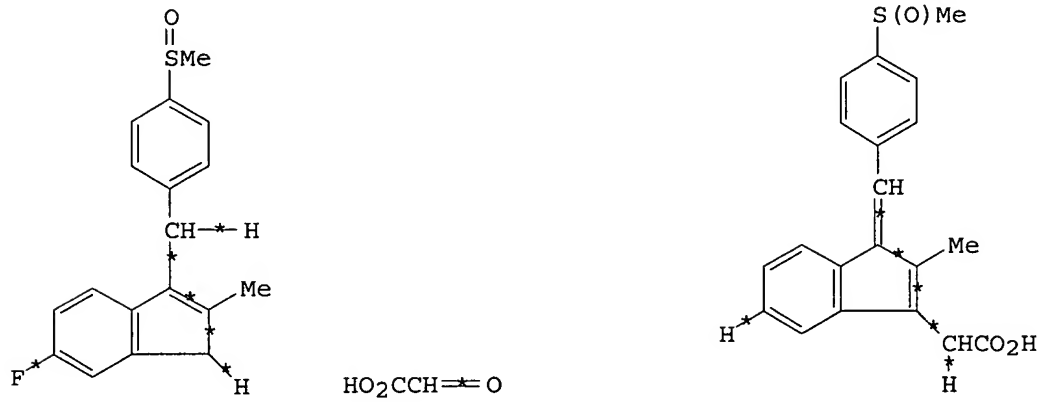
RX(1) OF 3 A ===> B...



II (1) III
YIELD 56.0%

RX(1) RCT II, 805178
RGT 471 (80-15-9), Ph-CMe2-O-OH
1283 (546-68-9), Ti(O-iPr)4
1190 (87-91-2;13811-71-7;21066-72-8;57968-71-5;122406-96-6;128851-23-0), CHIRAL, (+)-diethyl tartrate
222 (7732-18-5), H2O
SOL 60 (75-09-2), CH2Cl2
PRO III, 805179, (R)-isomer
YDS 56.0 %
T -30.0 Cel
EEXP 1 91.0 %
NTE reaction:II -> (R)-III

RX(2) OF 3 ...B + H ===> I



III IV (2) V
YIELD 30.0%

RX(2) RCT III, **805179**, (R)-isomer
IV, 8876 (298-12-4)
RGT **904** (100-85-6), Triton B
SOL 222 (7732-18-5), H2O
123 (67-56-1), MeOH

```
PRO  V, 805180, (R)-isomer
YDS  30.0 %
T    50.0 Cel
KW   alkylation; C-alkylation
NTE  reaction:(R)-III (IV) -> (R)-V
```

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=> d iall abeq tech abex hitstr 40
YOU HAVE REQUESTED DATA FROM FILE 'CHEMINFORMRX, WPIX, HCAPLUS, USPATFULL,
TOXCENTER, IFICDB' - CONTINUE? (Y)/N:y
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```
L90  ANSWER 40 OF 40  WPIX  COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER:     2002-507896 [54]   WPIX
DOC. NO. CPI:         C2002-144362
TITLE:                Use of nitro derivatives as drugs for treating pre-cancer
                      or cancer diseases having inflammatory basis e.g.
                      colitis, gastritis, enteritis, duodenitis, hepatopathies.
DERWENT CLASS:        B05
INVENTOR(S):          ANTOGNAZZA, P; BENEDINI, F; DEL SOLDATO, P
PATENT ASSIGNEE(S):   (NICO-N) NICOX SA; (ANTO-I) ANTOGNAZZA P; (BENE-I)
                      BENEDINI F; (DSOL-I) DEL SOLDATO P
COUNTRY COUNT:        86
PATENT INFORMATION:
```

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2002030866	A1	20020418	(200254)*	EN	72	C07C203-04
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW						
W: AE AG AL AU BA BB BG BR BZ CA CN CR CU CZ DM DZ EE GD GE HR HU ID IL IN IS JP KP KR LC LK LR LT LV MA MG MK MN MX NO NZ PL RO SG SI SK TR TT UA US UZ VN YU ZA						
AU 2002015932	A	20020422	(200254)			C07C203-04
EP 1339665	A1	20030903	(200365)	EN		C07C203-04
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR						
IT 1319202	B	20030926	(200409)			A61K031-00
US 2004023933	A1	20040205	(200411)			A61K031-60
JP 2004511455	W	20040415	(200426)		129	C07C203-04

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002030866	A1	WO 2001-EP11664	20011009
AU 2002015932	A	AU 2002-15932	20011009
EP 1339665	A1	EP 2001-986670	20011009
		WO 2001-EP11664	20011009
IT 1319202	B	IT 2000-MI2202	20001012
US 2004023933	A1	WO 2001-EP11664	20011009
		US 2003-398289	20030410
JP 2004511455	W	WO 2001-EP11664	20011009
		JP 2002-534255	20011009

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2002015932 A Based on WO 2002030866
EP 1339665 A1 Based on WO 2002030866
JP 2004511455 W Based on WO 2002030866

PRIORITY APPLN. INFO: IT 2000-MI2202 20001012
INT. PATENT CLASSIF.:
MAIN: A61K031-00; A61K031-60; C07C203-04
SECONDARY: A61K031-192; A61K031-21; A61K031-22; A61K031-222; A61K031-223; A61K031-235; A61K031-44; A61P001-00; A61P001-04; A61P001-16; A61P029-00; A61P035-00; C07C233-25; C07C233-54; C07C317-44; C07C317-46; C07C323-60; C07C327-34; C07D201-02; C07D213-34

BASIC ABSTRACT:
WO 200230866 A UPAB: 20020823
NOVELTY - Treatment of pre-cancer or cancer diseases on an inflammatory basis involves the use of nitro derivatives or their salts.
DETAILED DESCRIPTION - Treatment of pre-cancer or cancer diseases on an inflammatory basis involves the use of nitro derivatives of formula A-X1-L-(W)p-NO2 (I) or their salts.
s, p, t, t' = 1 or 0;
A = R-T1;
R = 5-fluoro-1-(4-methanesulfinyl-benzylidene)-2-methyl-1H-indene-3-yl methyl or group of formula (II);
Rai, R1f = H, CH3;
R1 = OCOR3, NHCOR3, OH, CH2CH(CH3)2, phenyl, benzoyl, 4,6-dichlorophenyl amino;
R3 = 1-5C radical;
R6 = H or halo (preferably F);
R1+R6 at position 4 and 5 = group of formula (IIa);
T'1, T1 = (CO)t or (X)t';
X = O, S, NR1c;
R1c = H or 1-5C alkyl;
X1 = -TB-Y-T'1;
TB = CO or X;
Y = -Q-y3-Q'-, T, 5-7C cycloalkylene optionally substituted by (T or heteroatoms), groups of formula (III), (IV) or (V), -Z-(O-Z)NF, -Z'-(O-Z')nf, -Z-(O-Z)nf, -Z'-(O-Z')nf;
Q = RTIX-(c)nIX-RTIX'; Q = RTIIX-(c)nIIX-RTIIX';
T = 1-20C (preferably 2-6C)alkylene optionally substituted by -NHCOR3, -NH2 or -OH;
Z = -CH(ONO2)-CH(R1f)-CH2;
Z' = -CH2-CH(ONO2)-CH2;
Z = -CH(R1f)-CH2;
Z' = -CH2-Cl+(R1f);
nIX = 0 - 3 (preferably 1);
nIIX = 1 - 3 (preferably 1);
RTIX, RTIX', TTIIX, RTIIX' = H or 1-4C alkyl (preferably H);
n3 = 0-3;
n3' = 1-3;
R4 = OH, H or R5O-alkoxy;
R5 = 1-10C (cyclo)alkyl (preferably methyl);
R2 = 2-10C alkylene with at least one double bond (preferably ethenylene);
nf = 0-6 (preferably 0-4);
L = covalent bond, X or CO; and
W = YO.
Provided that:
when t = 1 then t' = 0 and when t = 0 then t' = 1 and
when T = O then TB = CO and when T' = O the TB = X.
ACTIVITY - Cytostatic; Antiinflammatory; Antitumor.

MECHANISM OF ACTION - Proliferation of cancerous cell inhibitor.

Human adenocarcinoma cells were sown on plates and the plates were inoculated with 2-hydroxybenzoic acid 3-(nitrooxy methyl)phenyl ester (C) dissolved in dimethylsulfoxide (DMSO) at 200 micro M concentration. Some plates were treated with (C) dissolved in DMSO (200 micro M concentration) in presence of a solution of cisplatinum (25 micro M). After 15 hours of incubation the plates were put into contact with a solution of 3H-timidine (1 approx. MG/mol). The cell monolayer of each plate was first washed twice with a cold saline buffer, then treated with trichloroacetic acid (TCA) at 5% for 10 minutes and then washed three times with absolute alcohol. The cells were dissolved in 0.1N sodium hydroxide (NaOH) (500 micro l) and the incorporated radioactivity was determined. The % of 3H-timidine incorporated in the cells for control/test compound (C) without cisplatinum was 438/246 respectively and with 25 micro M cisplatinum was 100/50 respectively.

USE - For preparing drugs for treating pre-cancer or cancer diseases on an inflammatory basis affecting the digestive apparatus preferably the intestinal tract e.g. colitis, gastritis, enteritis, duodenitis, hepatopathies and tumoral processes; and for the prevention and/or treatment of tumoral diseases (claimed). The pathologies on an inflammatory basis can involve various systems e.g. urogenital, respiratory, skin, digestive system etc.

ADVANTAGE - The compounds are not toxic to the digestive apparatus and prevent or reduce the diseases affecting the digestive apparatus. The paracetamol nitro oxy derivatives are not only effective as analgesic drugs but also have no hepatic toxicity and are bale to prevent or reduce the already existing hepatic damages.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B07-H; B10-A05; B14-C03; B14-H01; B14-K01; B14-L06; B14-N17
ABEX UPTX: 20020823

SPECIFIC COMPOUNDS - 40 Compounds are specifically claimed as (I). e.g. 2-(hydroxy)benzoic acid 3-(nitroxymethyl)phenyl ester.

ADMINISTRATION - The compounds are administered in combination with chemotherapeutic drugs or in the radiotherapeutic treatment (claimed). Administration is parenteral, oral or topical.

EXAMPLE - 3-Hydroxymethylphenol (10 g, 0.08 moles) was dissolved in toluene (50 ml) containing triethylamine (9.8 g, 0.1 moles) and acetylsalicylic acid chloride solution (16 g, 0.08 moles) in toluene (50 ml) was added under stirring at 5 - 10degreesC. The mixture was maintained within 5 - 10degreesC under stirring for 2 hours, then poured into water and then extracted with dichloromethane. After work up, 3-hydroxymethyl phenyl ester of 2-acetoxybenzoic acid (A) was obtained. A solution of fuming nitric acid (3.92 g) and sulfuric acid (3.92 g) and sulfuric acid 96% (6.10 g) in dichloromethane (25 ml) was cooled to 0degreesC and added in over an hour under stirring and under nitrogen atmosphere to a solution of (A) (6 g, 20.7 mmoles) in dichloromethane (25 ml). The mixture was then diluted with dichloromethane (50 ml) and poured into water and ice (100 g). After work up, 3-nitrooxymethylphenyl ester of the 2-(acetyloxy)benzoic acid (B) was obtained. Methanol (5 ml) and water (4 ml), imidazole (0,04 g, 0.6 mmoles) was added to a solution of (B) (2 g, 6.04 mmoles) in tetrahydrofuran (THF) (10 ml). The mixture was left under stirring at room temperature for 20 days and then the solvent was evaporated at reduced pressure. After work up, 2-hydroxybenzoic acid 3-(nitrooxy methyl)phenyl ester (C) (0.8 g) (yield 46%) was obtained.

DEFINITIONS - Preferred Definitions:

R = acetyl salicylic acid, salicylic acid, paracetamol, ibuprofen, flurbiprofen, sulindac, naproxen, ketoprofen, diclofenac;
y3 - pyridyl.
(1) when s = 0 and R6 = H then:
(i) R1 is U or U', -T1-TB- is V, Y is a group of formula (III) with n3 being 0 and n3' being 1, -Q-y3-Q' with y3 being pyridyl or -Z-(O-Z)nf with R1f being H and nf being 1, T'1 is -O-, L is covalent bond and p is 0, or
(ii) R1 is U or U', -T1-TB- is V, Y is a group of formula (V) with R4 being methoxyl and R2 being -CH=CH-, -T'1-L- is V, p is 1 and W is yO with y being -(CH2)4- or -(CH2)3-, or
(iii) R1 is u', -T1-TB- is v', y is -(CH2)3-, T'1-L is -O-(L is a covalent bond) and p is o, or
(iv) R1 is u', -T1-TB- is v', y is an ethylene group substituted with -CH(NHCOCH3)-CH2-, -T'1-L- is -S-CO-, p is 1 and W is yO with y being -(CH2)3-.
U is acetyloxy or hydroxyl at the position.
U' is acetylamino at the fourth position.
V is -CO-O or -O-OC-ester.
V' is -O-CO-.
(2) when s = 1 then R6 = H or F at third position, R1 is CH2CH(CH3)2 or phenyl at fourth position, -T1-TB is -CO-O-ester, Y is a group of formula (V) with R4 being methoxy and R2 being -CH=CH-T'1-L- is -CO-O, p is 1 and W is yO with y being -(CH2)3.
(3) when R = 5-fluoro-1-(4-methanesulfinyl-benzylidene)-2-methyl-1H-inden-3-yl methyl, then -T1-TB- is -CO-O-, y is -Q-y3-Q'- or -(CH2)4- with y3 being pyridyl, -T'1 is -O-, L is a covalent bond and p is O.

DCSE 570042-0-1-0
CN.S [6-Fluoro-3-(4-methanesulfinyl-benzylidene)-2-methyl-3H-inden-1-yl]-acetic acid 6-nitrooxymethyl-pyridin-2-ylmethyl ester; compound with GENERIC INORGANIC NEUTRAL COMPONENT
SDCN RA7NQ1

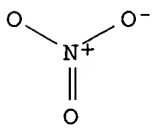
CM 1

Cl

CM 2

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *
DCSE 570041-0-0-0
SDCN RA7NQ0

CM 1



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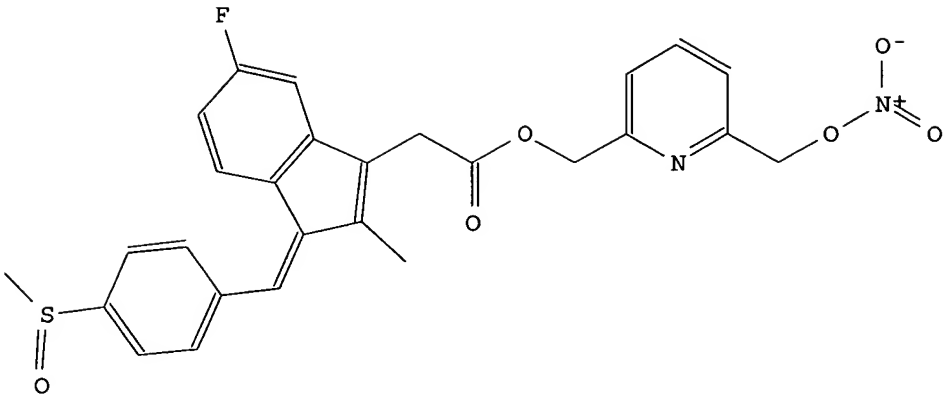
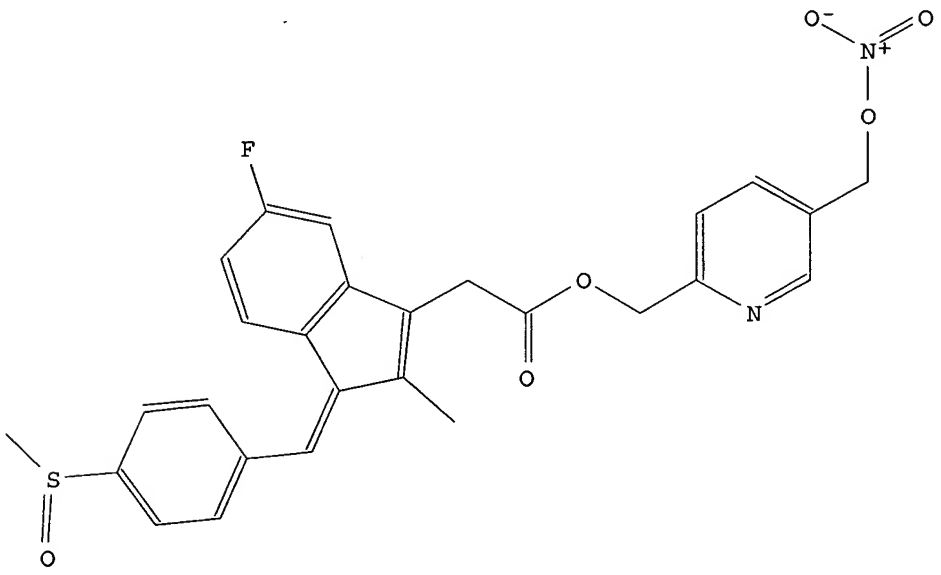


DCSE 570040-0-1-0
CN.S [6-Fluoro-3-(4-methanesulfinyl-benzylidene)-2-methyl-3H-inden-1-yl]-acetic acid 5-nitrooxymethyl-pyridin-2-ylmethyl ester; compound with GENERIC INORGANIC NEUTRAL COMPONENT
SDCN RA7NPZ

CM 1

Cl

CM 2



DCSE 570039-0-0-0
SDCN RA7NPY

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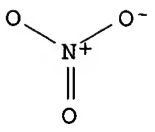

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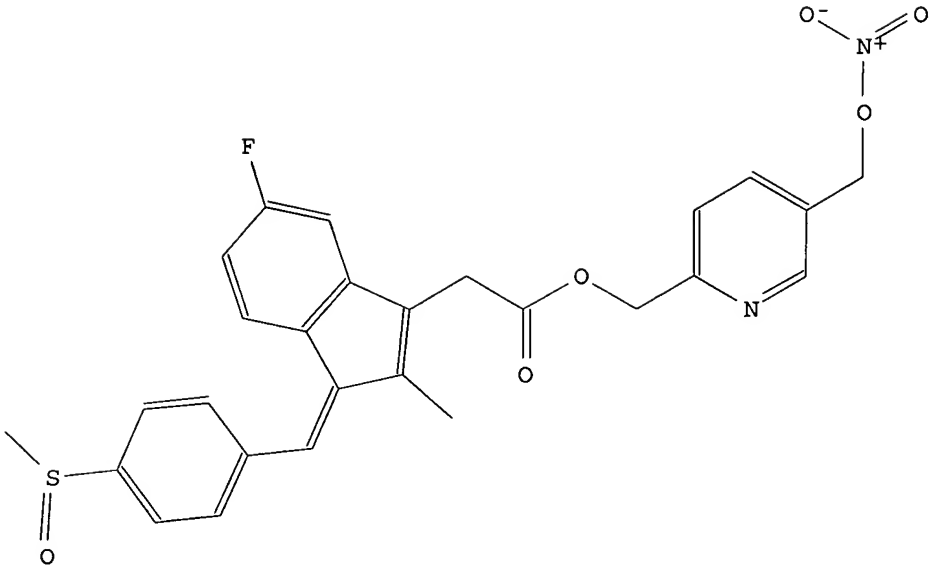

DCSE 570038-0-0-0
SDCN RA7NPX

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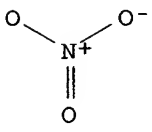

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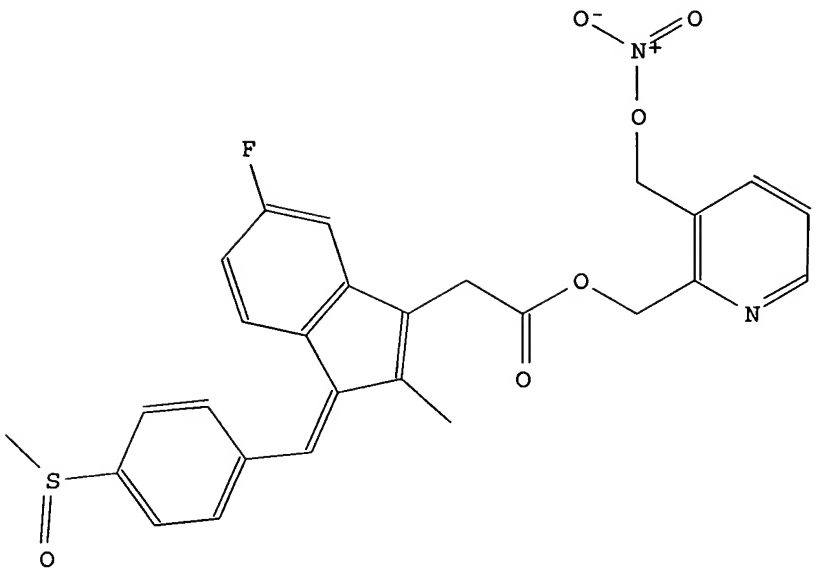
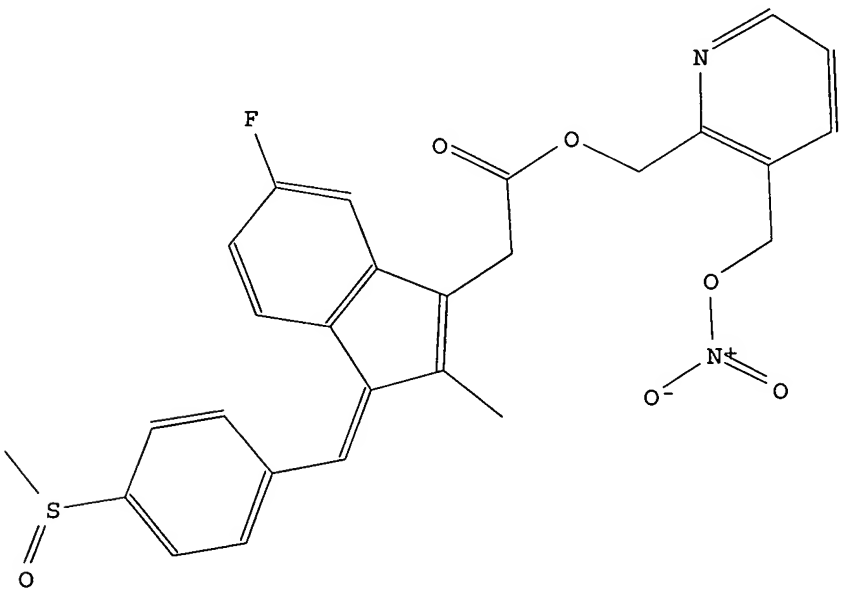


DCSE 570037-0-1-0
CN.S [6-Fluoro-3-(4-methanesulfinyl-benzylidene)-2-methyl-3H-inden-1-yl]-acetic acid 3-nitrooxymethyl-pyridin-2-ylmethyl ester; compound with GENERIC INORGANIC NEUTRAL COMPONENT
SDCN RA7NPW

CM 1

Cl

CM 2

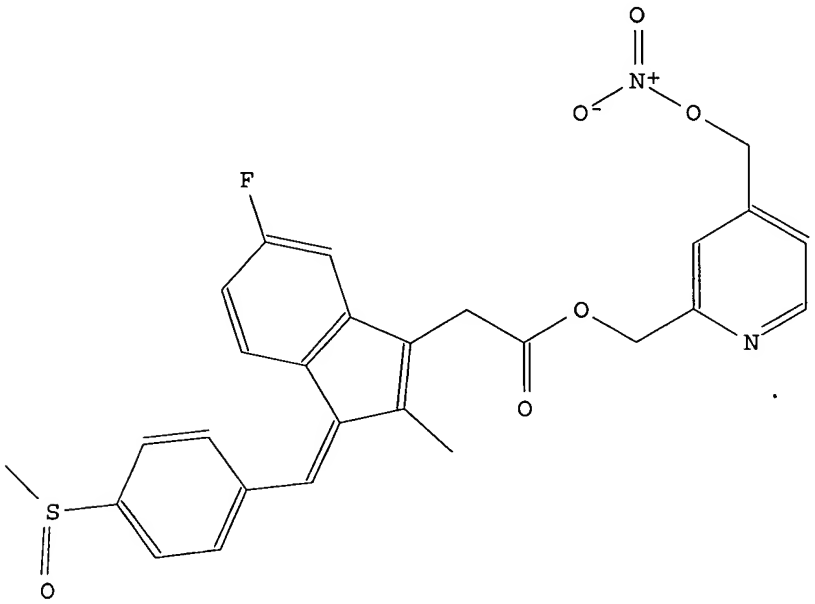


DCSE 570036-0-1-0
CN.S [6-Fluoro-3-(4-methanesulfinyl-benzylidene)-2-methyl-3H-inden-1-yl]-acetic acid 4-nitrooxymethyl-pyridin-2-ylmethyl ester; compound with GENERIC INORGANIC NEUTRAL COMPONENT
SDCN RA7NPV

CM 1

Cl

CM 2



DCSE 570035-0-0-0
SDCN RA7NPU

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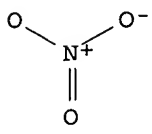

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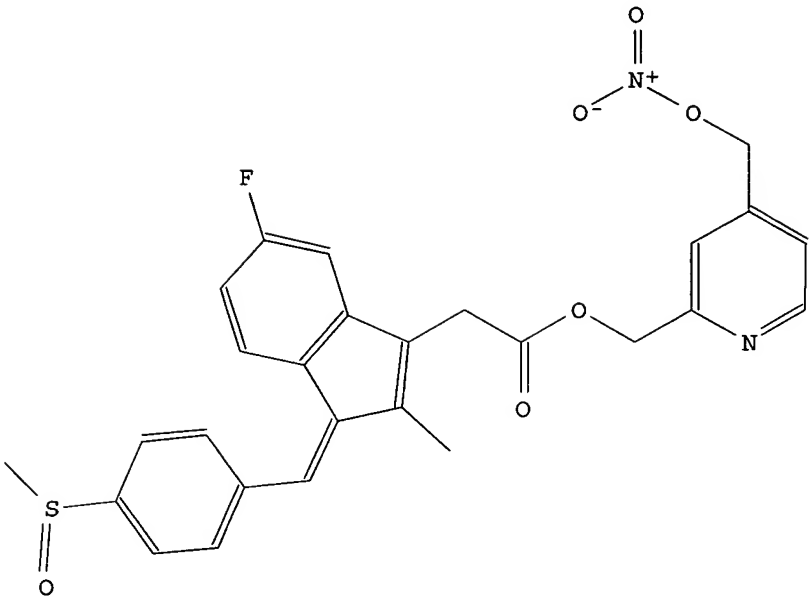

=> file stnguide
FILE 'STNGUIDE' ENTERED AT 11:49:38 ON 27 MAR 2006
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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Mar 24, 2006 (20060324/UP).

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=> d his l88

     (FILE 'HCAPLUS, WPIX, TOXCENTER' ENTERED AT 11:35:55 ON 27 MAR 2006)
L88           9 S L86-L87 AND (FLOR? OR FLA OR FL)/SO,CS,PA

=> d que l88
L69              QUE  ABB=ON  PLU=ON  MSRA OR MSRB OR (?METHIONIN?(5A)?RED
                 UCTAS?)
L72              QUE  ABB=ON  PLU=ON  WEISSBACH, H?/AU
L73              QUE  ABB=ON  PLU=ON  BROT, N?/AU
L85         585 SEA (L72 OR L73)
L86          68 SEA L85 AND (?SULFID? OR ?SULFOX?)
L87          55 SEA L85 AND L69
L88           9 SEA (L86 OR L87) AND (FLOR? OR FLA OR FL)/SO,CS,PA


=> d his l81

     (FILE 'MEDLINE, BIOSIS, PASCAL, JICST-EPLUS, CABA, LIFESCI, EMBASE,
     DRUGU, DRUGB, VETU, VETB, SCISEARCH, CONF, CONFSCI, DISSABS' ENTERED AT
     11:14:33 ON 27 MAR 2006)
L81          50 S L78 OR L80

=> d que l81
L66              QUE  ABB=ON  PLU=ON  ?OXIDAS?
L67              QUE  ABB=ON  PLU=ON  ?NEURODEGEN? OR (NEURO(1W)DEGEN?) OR
                  (NEURON(3A)DEGEN?) OR ?ALZHEIM? OR ANTIALZHEIM? OR PARKI
                 NSON? OR ANTIPARKINSON? OR (AMYTROPH?(3A)?SCLER?) OR STRO
                 KE OR (HEART(1W)ATTACK) OR ?INFARCT? OR ?ISCHEM?
L68              QUE  ABB=ON  PLU=ON  ?CARDIO? OR ?PULMON? OR ?VASCUL? OR
                 ?CORONAR? OR ?CARDIAC? OR ?IMMUN? OR AUTOIMMUN? OR AGING
                 OR AGE
L69              QUE  ABB=ON  PLU=ON  MSRA OR MSRB OR (?METHIONIN?(5A)?RED
                 UCTAS?)
L72              QUE  ABB=ON  PLU=ON  WEISSBACH, H?/AU
L73              QUE  ABB=ON  PLU=ON  BROT, N?/AU
L76         1382 SEA (L72 OR L73)
L77          389 SEA L76 AND (L66 OR L67 OR L68 OR L69)
L78           50 SEA L77 AND (FLA OR FLOR? OR FL)/SO,CS,PA
L79          188 SEA L77 AND (L66 OR L69)
L80           49 SEA L78 AND L79
L81           50 SEA L78 OR L80


=> dup rem l88 l81
DUPLICATE IS NOT AVAILABLE IN 'CONF'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
FILE 'HCAPLUS' ENTERED AT 11:50:28 ON 27 MAR 2006
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FILE 'TOXCENTER' ENTERED AT 11:50:28 ON 27 MAR 2006
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FILE 'MEDLINE' ENTERED AT 11:50:28 ON 27 MAR 2006
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FILE 'BIOSIS' ENTERED AT 11:50:28 ON 27 MAR 2006

FILE 'PASCAL' ENTERED AT 11:50:28 ON 27 MAR 2006

FILE 'LIFESCI' ENTERED AT 11:50:28 ON 27 MAR 2006

FILE 'EMBASE' ENTERED AT 11:50:28 ON 27 MAR 2006

FILE 'DRUGU' ENTERED AT 11:50:28 ON 27 MAR 2006

FILE 'SCISEARCH' ENTERED AT 11:50:28 ON 27 MAR 2006

FILE 'CONFSCI' ENTERED AT 11:50:28 ON 27 MAR 2006

PROCESSING COMPLETED FOR L88
PROCESSING COMPLETED FOR L81
L91 28 DUP REM L88 L81 (31 DUPLICATES REMOVED)
ANSWERS '1-6' FROM FILE HCAPLUS
ANSWERS '7-8' FROM FILE TOXCENTER
ANSWERS '9-12' FROM FILE BIOSIS
ANSWER '13' FROM FILE DRUGU
ANSWERS '14-27' FROM FILE SCISEARCH
ANSWER '28' FROM FILE CONFSCI

=> file stnguide
FILE 'STNGUIDE' ENTERED AT 11:50:37 ON 27 MAR 2006

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Mar 24, 2006 (20060324/UP).

=> d ibib ed ab 1-28
YOU HAVE REQUESTED DATA FROM FILE 'BIOSIS, DRUGU, SCISEARCH, CONFSCI, HCAPLUS, TOXCENTER' - CONTINUE? (Y)/N:y

L91 ANSWER 1 OF 28 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2005:69791 HCAPLUS
DOCUMENT NUMBER: 142:214058
TITLE: **Methionine sulfoxide reductases**: history and cellular role in protecting against oxidative damage
AUTHOR(S): **Weissbach, Herbert**; Resnick, Lionel; **Brot, Nathan**
CORPORATE SOURCE: Center for Molecular Biology and Biotechnology, **Florida** Atlantic University, Boca Raton, **FL**, 33431, USA
SOURCE: Biochimica et Biophysica Acta, Proteins and Proteomics (2005), 1703(2), 203-212
CODEN: BBAPBW; ISSN: 1570-9639
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 26 Jan 2005
AB A review. An enzyme that can reduce methionine **sulfoxide** in proteins was 1st discovered in Escherichia coli .apprx.25 years ago. It is now apparent that there is a family of enzymes, referred to as **methionine sulfoxide reductases** (Msrs), and in recent years there has been considerable interest in one of the members of the Msr family, **MsrA**. This enzyme has been shown to protect cells against oxidative damage, which suggests a possible role in a large number of age-related diseases. This review summarizes the history of the discovery of **MsrA**, properties of the enzyme, and its role in protecting cells against oxidative damage. Other members of the Msr family that differ in substrate specificity and localization are also described as well as a possible role for the Msr system in drug metabolism The concept that the Msr system can be used to develop novel drugs that could be catalytic antioxidants is discussed.
REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 2 OF 28 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2004:467703 HCAPLUS
DOCUMENT NUMBER: 141:28644
TITLE: Catalytic antioxidants and methods of use
INVENTOR(S): **Weissbach, Herbert; Brot, Nathan**
PATENT ASSIGNEE(S): **Florida Atlantic University, USA**; Hospital for Special Surgery
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004047772	A2	20040610	WO 2003-US38817	20031126
WO 2004047772	A3	20040715		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,
TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004143016 A1 20040722 US 2003-723809 20031126
PRIORITY APPLN. INFO.: US 2002-429269P P 20021126
OTHER SOURCE(S): MARPAT 141:28644
ED Entered STN: 10 Jun 2004
AB The invention provides small mols. that act as catalytic antioxidants and methods of use thereof. The compds. can repeatedly bind and destroy reactive oxygen species by serving as substates for enzymes of the **methionine sulfoxide reductase** (Msr) class.
Some embodiments of the catalytic antioxidant compds. are derived from drugs with anti-inflammatory activity due to inhibition of cyclooxygenase enzymes.

L91 ANSWER 3 OF 28 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2003:940007 HCAPLUS
DOCUMENT NUMBER: 140:156689
TITLE: Reduction of Sulindac to its active metabolite, sulindac **sulfide**: assay and role of the **methionine sulfoxide reductase** system
AUTHOR(S): Etienne, Frantzy; Resnick, Lionel; Sagher, Daphna; **Brot, Nathan; Weissbach, Herbert**
CORPORATE SOURCE: Center for Molecular Biology and Biotechnology, **Florida** Atlantic University, Boca Raton, **FL**, USA
SOURCE: Biochemical and Biophysical Research Communications (2003), 312(4), 1005-1010
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 03 Dec 2003
AB Sulindac is a known anti-inflammatory drug that functions by inhibition of cyclooxygenases 1 and 2 (COX). There has been recent interest in Sulindac and other non-steroidal anti-inflammatory drugs (NSAID) because of their anti-tumor activity against colorectal cancer. Studies with sulindac have indicated that it may also function as an anti-tumor agent by stimulating apoptosis. Sulindac is a pro-drug, containing a Me **sulfoxide** group, that must be reduced to sulindac **sulfide** to be active as a COX inhibitor. In the present studies the authors have developed a simple assay to measure sulindac reduction and tested sulindac as a substrate for 6 known members of the **methionine sulfoxide reductase** (Msr) family that have been identified in Escherichia coli. Only **MsrA** and a membrane associated Msr can reduce sulindac to the active **sulfide.** The reduction of sulindac also has been demonstrated in exts. of calf liver, kidney, and brain. Sulindac reductase activity is also present in mitochondria and microsomes.
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 4 OF 28 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2002:971998 HCAPLUS

DOCUMENT NUMBER: 139:2756
TITLE: A **methionine sulfoxide reductase** in Escherichia coli that reduces the R enantiomer of methionine **sulfoxide**
AUTHOR(S): Etienne, Frantzy; Spector, Daniel; **Brot, Nathan; Weissbach, Herbert**
CORPORATE SOURCE: Center for Molecular Biology and Biotechnology, **Florida** Atlantic University, Boca Raton, **FL**, 33431, USA
SOURCE: Biochemical and Biophysical Research Communications (2003), 300(2), 378-382
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 24 Dec 2002
AB It is known that Escherichia coli methionine mutants can grow on both enantiomers of methionine **sulfoxide** (met(o)), i.e., met-R-(o) or met-S-(o), indicating the presence of enzymes in E. coli that can reduce each of these enantiomers to methionine (met). Previous studies have identified two members of the **methionine sulfoxide reductase** (Msr) family of enzymes, **MsrA** and fSMsr, that could reduce free met-S-(o), but the reduction of free met-R-(o) to met has not been elucidated. One possible candidate is **MsrB** which is known to reduce met-R-(o) in proteins to met. However, free met-R-(o) is a very poor substrate for **MsrB** and the level of **MsrB** activity in E. coli exts. is very low. A new member of the Msr family (fRMsr) has been identified in E. coli exts. that reduces free met-R-(o) to met. Partial purification of FRMsr has been obtained using exts. from an **MsrA/MsrB** double mutant of E. coli.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 5 OF 28 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 2003:144283 HCAPLUS
DOCUMENT NUMBER: 139:97166
TITLE: New membrane-associated and soluble peptide **methionine sulfoxide reductases** in Escherichia coli
AUTHOR(S): Spector, Daniel; Etienne, Frantzy; **Brot, Nathan; Weissbach, Herbert**
CORPORATE SOURCE: Center for Molecular Biology and Biotechnology, **Florida** Atlantic University, Boca Raton, **FL**, 33431, USA
SOURCE: Biochemical and Biophysical Research Communications (2003), 302(2), 284-289
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 26 Feb 2003
AB It is known that reactive oxygen species can oxidize methionine residues in proteins in a non-stereospecific manner, and cells have mechanisms to reverse this damage. **MsrA** and **MsrB** are members of the methionine **sulfoxide** family of enzymes that specifically reduce the S and R forms, resp., of methionine **sulfoxide** (met(o)) in proteins. However, in Escherichia coli the level of **MsrB** activity is very low, which suggested that there may be other enzymes capable of reducing the R epimer of met(o) in proteins. Employing a **msrA**/B double mutant, a new peptide **methionine**

sulfoxide reductase activity has been found associated with membrane vesicles from E. coli. Both the R and S forms of N-acetyl-met(o), D-ala-met(o)-enkephalin and met(o), are reduced by this membrane associated activity. The reaction requires NADPH and may explain, in part, how the R form of met(o) in proteins is reduced in E. coli. In addition, a new soluble Msr activity was also detected in the soluble exts. of the double mutant that specifically reduces the S epimer of met(o) in proteins.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 6 OF 28 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 2002:43848 HCAPLUS
DOCUMENT NUMBER: 136:163059
TITLE: Peptide **methionine sulfoxide reductase**: Structure, mechanism of action, and biological function
AUTHOR(S): **Weissbach, Herbert**; Etienne, Frantzy; Hoshi, Toshinori; Heinemann, Stefan H.; Lowther, W. Todd; Matthews, Brian; St. John, Gregory; Nathan, Carl; **Brot, Nathan**
CORPORATE SOURCE: Center for Molecular Biology and Biotechnology, **Florida** Atlantic University, Boca Raton, **FL**, 33431, USA
SOURCE: Archives of Biochemistry and Biophysics (2002), 397(2), 172-178
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 17 Jan 2002
AB A review with 40 refs. Reactive O and N intermediates can cause damage to many cellular components and have been implicated in a number of diseases. Cells have developed a variety of mechanisms to destroy these reactive mols. or repair the damage once it occurs. In proteins, one of the amino acids most easily oxidized is methionine, which is converted to methionine **sulfoxide.** The enzyme, peptide **methionine sulfoxide reductase** (I), catalyzes the reduction of **methionine sulfoxide** in proteins back to methionine. There is growing evidence that I plays an important role in protecting cells against oxidative damage. This paper reviews the biochem. properties and biol. role of I. (c) 2002 Academic Press.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 7 OF 28 TOXCENTER COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2005:196118 TOXCENTER
DOCUMENT NUMBER: PubMed ID: 15914630
TITLE: **Methionine sulfoxide reductases** B1, B2, and B3 are present in the human lens and confer oxidative stress resistance to lens cells
AUTHOR(S): Marchetti Maria A; Pizarro Gresin O; Sagher Daphna; Deamicis Candida; **Brot Nathan**; Hejtmancik J Fielding; **Weissbach Herbert**; Kantorow Marc
CORPORATE SOURCE: **Department of Biomedical Science, Florida Atlantic University, Boca Raton, 33431, USA**
CONTRACT NUMBER: EY13022 (NEI)
SOURCE: Investigative ophthalmology & visual science, (2005 Jun) Vol. 46, No. 6, pp. 2107-12.

Journal code: 7703701. ISSN: 0146-0404.
COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 2005271813
LANGUAGE: English
ENTRY DATE: Entered STN: 20050726
Last Updated on STN: 20050726
ED Entered STN: 20050726
Last Updated on STN: 20050726
AB PURPOSE: **Methionine-sulfoxide reductases** are unique, in that their ability to repair oxidized proteins and **MsrA**, which reduces S-methionine **sulfoxide**, can protect lens cells against oxidative stress damage. To date, the roles of MsrB1, -B2 and -B3 which reduce R-methionine **sulfoxide** have not been established for any mammalian system. The present study was undertaken to identify those **MsrBs** expressed by the lens and to evaluate the enzyme activities, expression patterns, and abilities of the identified genes to defend lens cells against oxidative stress damage. METHODS: Enzyme activities were determined with bovine lens extracts. The identities and spatial expression patterns of MsrB1, -B2, and -B3 transcripts were examined by RT-PCR in human lens and 21 other tissues. Oxidative stress resistance was measured using short interfering (si)RNA-mediated gene-silencing in conjunction with exposure to tert-butyl hydroperoxide (tBHP) and MTS viability measurements in SRA04/01 human lens epithelial cells. RESULTS: Forty percent of the Msr enzyme activity present in the lens was **MsrB**, whereas the remaining enzyme activity was **MsrA**. MsrB1 (selenoprotein R, localized in the cytosol and nucleus), MsrB2 (CBS-1, localized in the mitochondria), and MsrB3 (localized in the endoplasmic reticulum and mitochondria) were all expressed by the lens. These genes exhibit asymmetric expression patterns between different human tissues and different lens sublocations, including lens fibers. All three genes are required for lens cell viability, and their silencing in lens cells results in increased oxidative-stress-induced cell death. CONCLUSIONS: The present data suggest important roles for both **MsrA** and -Bs in lens cell viability and oxidative stress protection. The differential tissue distribution and lens expression patterns of these genes, coupled with increased oxidative-stress-induced cell death on their deletion provides evidence that they are important for lens cell function, resistance to oxidative stress, and, potentially, cataractogenesis.

L91 ANSWER 8 OF 28 TOXCENTER COPYRIGHT 2006 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 1984:63972 TOXCENTER
COPYRIGHT: Copyright (c) 2006 The Thomson Corporation
DOCUMENT NUMBER: PREV198427083195
TITLE: REACTIVATION BY ESCHERICHIA-COLI **METHIONINE** SULF OXIDE PEPTIDE **REDUCTASE** OF ALPHA-1 ANTI TRYPSIN INACTIVATED BY CIGARETTE SMOKE AND HYDROGEN PER OXIDE
AUTHOR(S): JAMES H L [Reprint author]; **BROT N**; JANOFF A; CARP H; FLISS H; **WEISSBACH H**; COHEN A B
CORPORATE SOURCE: UNIV TEX HEALTH CENT TYLER, TYLER, TX, USA
SOURCE: American Review of Respiratory Disease, (1984) Vol. 129, No. 4 SUPPL, pp. A163.
Meeting Info.: 80TH ANNUAL MEETING OF THE AMERICAN LUNG ASSOCIATION, 79TH ANNUAL MEETING OF THE AMERICAN THORACIC SOCIETY, AND 72ND ANNUAL MEETING OF THE CONGRESS OF LUNG ASSOCIATION STAFF, MIAMI BEACH, FLA., USA, MAY. 20-23, 1984. AM REV RESPIR DIS
CODEN: ARDSBL. ISSN: 0003-0805.

DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BIOSIS
OTHER SOURCE: BIOSIS 1984:166703
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116
ED Entered STN: 20011116
Last Updated on STN: 20011116

L91 ANSWER 9 OF 28 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
DUPLICATE 5
ACCESSION NUMBER: 2005:524519 BIOSIS
DOCUMENT NUMBER: PREV200510314482
TITLE: **Methionine** sulfoxide **reductase**-A and sulindac protect **cardiac** myocytes against programmed death caused by hypoxia/reoxygenation or H202.
AUTHOR(S): Prentice, Howard M. [Reprint Author]; Resnick, Lionel; **Weissbach, Herbert**
CORPORATE SOURCE: **Florida Atlantic Univ, Boca Raton, FL 33431 USA**
SOURCE: Circulation, (OCT 26 2004) Vol. 110, No. 17, Suppl. S, pp. 189.
Meeting Info.: 77th Scientific Meeting of the American-Heart-Association. New Orleans, LA, USA. November 07 -10, 2004. Amer Heart Assoc.
CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Dec 2005
Last Updated on STN: 1 Dec 2005
ED Entered STN: 1 Dec 2005
Last Updated on STN: 1 Dec 2005
AB A major component of reperfusion injury involves oxidative damage to myocardial tissues caused by excess generation of reactive oxygen species (ROS). The principal targets are proteins, nucleic acids, and lipids. Methionine residues in proteins are oxidized by ROS to methionine sulfoxide. **Methionine** sulfoxide **reductase**-A (**MsrA**) is an antioxidant enzyme that specifically reduces methionine sulfoxide back to methionine reversing oxidative damage. Sulindac is an anti-inflammatory/antioxidant that is a selective target for **MsrA** and can function as a catalytic co-factor enhancing the reducing power of **MsrA**. We hypothesized that overexpression of **MsrA** or treatment with sulindac would protect neonatal rat **cardiac** myocytes against oxidative damage in models of reperfusion injury. Neonatal **cardiac** myocytes were subjected either to hypoxia-reoxygenation or to increasing doses of H2O2 and myocyte death was measured by DNA fragmentation, Hoechst and propidium iodide stains, or vital dye exclusion. Myocytes were infected with 20 plaque-forming units of adenovirus encoding **MsrA** and green fluorescent protein (AD-**MsrA**/GFP) or with a control AD-GFP virus. Infected myocytes were exposed to 20h hypoxia and 16h reoxygenation. In AD-GFP infected cultures 24 +/- 3.8% of myocytes displayed apoptotic markers after reoxygenation compared with 3.2 +/- 2.4% in normoxic controls ($p<0.05$; n=3). In AD-**MsrA**/GFP infected cultures apoptotic indices of reoxygenated myocytes were 15.8 +/- 1.2% ($p<0.01$; n=6). Therefore **MsrA** overexpression significantly decreased myocyte death (by >30%). Viability curves indicated an optimal sulindac concentration of 0.5 mM for **cardiac** myocytes. Myocytes were pre-treated with 0.5 mM sulindac and after 24h exposed to H2O2 (100-400 mu M) for a further 24h. There was a dose-dependent death of myocytes with a maximum kill of 68% at the

highest H2O2 concentration (n=3). Sulindac protected at all H2O2 concentrations with optimal protection of 44% and 57% at the 100 and 200 mu M levels respectively (n=3). These results may support therapeutic roles for **MsrA** or sulindac in protection against reperfusion injury of the heart.

L91 ANSWER 10 OF 28 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2006:47778 BIOSIS
DOCUMENT NUMBER: PREV200600056980
TITLE: Expression and localization of **methionine** sulfoxide **reductase** a in the retina.
AUTHOR(S): Gordiyenko, N. V. [Reprint Author]; Lee, J. W.; Marchetti, M.; Tserentsoodol, N.; Fariss, R. N.; **Weissbach, H.** ; Kantorow, M.; Rodriguez, R.
SOURCE: IOVS, (2005) Vol. 46, No. Suppl. S, pp. 5144. Meeting Info.: Annual Meeting of the Association-for-Research-in-Vision-and-Ophthalmology. Ft Lauderdale, **FL**, USA. May 01 -05, 2005. Assoc Res Vis & Ophthalmol. CODEN: IOVSDA. ISSN: 0146-0404.
DOCUMENT TYPE: Conference; (Meeting) Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Jan 2006 Last Updated on STN: 4 Jan 2006

ED Entered STN: 4 Jan 2006
Last Updated on STN: 4 Jan 2006

AB Purpose: To localize **msrA** in the monkey retina and cultured RPE cells and measure the effect of siRNA knockdown on the susceptibility of cultured RPE cells to oxidative stress. Methods: **MsrA** protein and mRNA expression were measured in monkey retina and cultured RPE cells by Northern and Western blot analyses. The **msrA** peptide was detected using a rabbit polyclonal anti-**msrA** antibody. Localization of **msrA** in monkey retina and cultured RPE cells was performed by fluorescent confocal microscopy using a Cy5 conjugated secondary antibody. **MsrA**-GFP fusion constructs were transfected into ARPE19 cells. SiRNA mediated gene silencing was conducted with separate siRNA sequences and RPE viability monitored by MTT assays in the presence or absence of increasing TBHP concentrations. Results: Northern blot analyses indicate **msrA** is expressed mainly in RPE with some expression in neural retina. In the RPE/Choroid **msrA** **immunoreactivity** was observed in bands at 28 kDa (actual size) and 150 kDa. In the neural retina and ARPE19 cells a similar to 50 kDa peptide was observed. **Immunohistochemical** analysis of the monkey retinal sections localized **msrA** in the apical side of the RPE as well as in the outer plexiform and inner nuclear layers. In cultured RPE cells endogenous **msrA** was localized in the mitochondria and cytosol. Transfection of the RPE cells with **msrA** -GFP fusion constructs corresponding to two different isoforms of **msrA** showed that full length of **msrA** localizing to the mitochondria, while the shorter transcript missing of the N-terminal sequence localized to the cytosol. SiRNA-mediated gene silencing of **msrA** resulted inloss of RPE viability with decreased resistance to oxidative stress. Conclusions: **MsrA** is localized mainly to the apical side of the RPE but is also present in the outer plexiform and inner nuclear layers of the retina. In the cultured RPE cells **msrA** is localized to the mitochondria and cytosol depending on the presence or absence of an alternatively spliced leader sequence. The large molecular weight sizes observed on Western blots suggest that

msrA is forming covalently bound complexes with itself and/or other proteins. Increased sensitivity to oxidative stress shown in cultured RPE cells after siRNA knockdown suggests **msrA** plays an important role in RPE survival and retinal function.

L91 ANSWER 11 OF 28 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2006:46248 BIOSIS
DOCUMENT NUMBER: PREV200600055449
TITLE: Three distinct human lens methionine sulfoxide B genes are important for lens cell viability and provide distinct levels of oxidative stress resistance.
AUTHOR(S): Marchetti, M. [Reprint Author]; Pizarro, G. O.; Sagher, D.; DeAmicis, C.; Lee, W.; Hejtmancik, J. F.; **Weissbach, H.**; Kantorow, M.
SOURCE: IOVS, (2005) Vol. 46, No. Suppl. S, pp. 3610.
Meeting Info.: Annual Meeting of the Association-for-Research-in-Vision-and-Ophthalmology. Ft Lauderdale, **FL**, USA. May 01 -05, 2005. Assoc Res Vis & Ophthalmol.
CODEN: IOVSDA. ISSN: 0146-0404.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Jan 2006
Last Updated on STN: 4 Jan 2006

ED Entered STN: 4 Jan 2006
Last Updated on STN: 4 Jan 2006

AB Purpose: Methionine sulfoxide accumulation is a major feature of **age** related cataract that can be repaired by a unique class of enzymes called **Methionine** sulfoxide **reductases** that act on R- and S-epimers of methionine sulfoxide (MSO).**MsrA** acts on S-MSO while three distinct **MsrBs** called B1, B2 and B3 act on R- MSO. Deletion of **MsrA** results in loss of lifespan in mice while overexpressionof **MsrA** provides lens and other cells resistance to oxidative stress. Here wesought to establish the range of **MsrB**'s expressed by the human lens and we evaluated the ability of the identified genes to confer oxidative stress resistance to human lens epithelial cells. Methods: RNA was extracted from microdissected bovine and human lenses and the enzyme activities, gene identities and spatial expression patterns of lens **MsrA** and **MsrB** genes were examined. The ability of the identified Msrs to resist oxidative stress was measured by siRNA-mediated gene silencing in conjunction with TBHP treatment and viability measurements in human SRA0411 lens cells. Corresponding levels of apoptosis were detected using TUNEL labeling. Results: Approximately 40% of the Msr activity in human lens epithelium and fibers is contributed by **MsrB.** Three separate **MsrB** genes are expressed by the human lens including MsrB1 (Selenoprotein R), MsrB2 (CBS-1) and MsrB3. These genes are variably expressed in different human tissues and lens sub-locations. Interestingly all the identified **MsrBs** are required for lens cell viability even in the absence of exogenous oxidative stress. **MsrA** and B2 are known to localize to the mitochondria and these Msrs but not B1 or B3 confer oxidative stress resistance to lens cells. Conclusions: These datademonstrate that the human lens contains both **MsrA** and **MsrB** activity and expresses **MsrA**, MsrB1, MsrB2 and MsrB3 genes. The varied expression of these genesin different tissues and lens sub-locations together with evidence for different activities of the proteins in providing resistance to oxidative stress suggest specialized roles for these genes in lens function, including resistance to oxidative stress and

potentially to cataract formation.

L91 ANSWER 12 OF 28 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1983:12134 BIOSIS
DOCUMENT NUMBER: PREV198324012134; BR24:12134
TITLE: LENS **METHIONINE** SULFOXIDE **REDUCTASE.**
AUTHOR(S): SPECTOR A [Reprint author]; **WEISSBACH H**; **BROT N**
CORPORATE SOURCE: COLUMBIA UNIV, NY 10032, USA
SOURCE: Investigative Ophthalmology and Visual Science, (1982) Vol. 22, No. 3 SUPPL, pp. 34.
Meeting Info.: **ANNUAL SPRING MEETING OF THE ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY INCORPORATED, SARASOTA, FLA., USA, MAY 2-7, 1982. INVEST OPHTHALMOL VISUAL SCI.**
CODEN: IOVSDA. ISSN: 0146-0404.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH

L91 ANSWER 13 OF 28 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN DUPLICATE 4
ACCESSION NUMBER: 2004-14432 DRUGU B P
TITLE: **Methionine** sulfoxide **reductase** A protects neuronal cells against brief hypoxia/reoxygenation.
AUTHOR: Yermolaieva O; Xu R; Schinstock C; **Brot N**; **Weissbach H**; Heinemann S H; Hoshi T
CORPORATE SOURCE: Univ.Iowa; Univ.Cornell; Univ.**Florida**-Atlantic; Univ.Jena; Univ.Pennsylvania
LOCATION: Iowa City, Iowa, New York, N.Y., Boca Raton, Fla.; Philadelphia, Pa., USA; Jena, Ger.
SOURCE: Proc.Natl.Acad.Sci.U.S.A. (101, No. 5, 1159-64, 2004) 4 Fig. 46 Ref.
CODEN: PNASA6 ISSN: 0027-8424
AVAIL. OF DOC.: Department of Physiology, University of Pennsylvania, Richards D100, 3700 Hamilton Walk, Philadelphia, PA 19104, U.S.A. (T.H.). (e-mail: hoshi@hoshi.org).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Overexpression of bovine **methionine** sulfoxide **reductase** type A (**MSRA**) using adenovirus vectors protected against increased levels of reactive oxygen species (ROS) and apoptosis in PC12 cells subjected to brief hypoxia/reoxygenation. The ROS scavenger TEMPOL also reduced the ROS levels in hypoxic cells. Hypoxia resulted in a depolarization of the mitochondrial membrane in intact PC12 cells and in isolated rat liver mitochondria. Results show that **MSRA** plays a protective role against hypoxia/reoxygenation-induced cell injury and suggest the therapeutic potential of **MSRA** in **ischemic** heart and brain disease.

L91 ANSWER 14 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:719139 SCISEARCH
THE GENUINE ARTICLE: 925KR
TITLE: **Methionine** sulfoxide **reductase**-a and **cardiac** myocyte protection against hypoxia/reoxygenation or H2O2

AUTHOR: Prentice H (Reprint); Resnick L; **Weissbach H**; Webster K A
CORPORATE SOURCE: **Florida Atlantic Univ, Boca Raton, FL 33431 USA**; Univ Miami, Miami, **FL** 33152 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY, (MAY 2005) Vol. 38, No. 5, pp. 828-828. MA 51.
ISSN: 0022-2828.
PUBLISHER: ACADEMIC PRESS LTD ELSEVIER SCIENCE LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0
ENTRY DATE: Entered STN: 22 Jul 2005
Last Updated on STN: 1 Dec 2005
ED Entered STN: 22 Jul 2005
Last Updated on STN: 1 Dec 2005

L91 ANSWER 15 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:298345 SCISEARCH
THE GENUINE ARTICLE: 904MN
TITLE: Biomarkers of oxidative stress study II. Are oxidation products of lipids, proteins, and DNA markers of CCl4 poisoning?
AUTHOR: Kadiiska M B (Reprint); Gladen B C; Baird D D; Germolec D; Graham L B; Parker C E; Nyska A; Wachsman J T; Ames B N; Basu S; **Brot N**; FitzGerald G A; Floyd R A; George M; Heinecke J W; Hatch G E; Hensley K; Lawson J A; Marnett L J; Morrow J D; Murray D M; Plastaras J; Roberts L J; Rokach J; Shigenaga M K; Sohal R S; Sun J; Tice R R; Van Thiel D H; Wellner D; Walter P B; Tomer K B; Mason R P; Barrett J C
CORPORATE SOURCE: NIEHS, US Dept HHS, NIH, POB 12233, MD F0-02, Res Triangle Pk, NC 27709 USA (Reprint); NIEHS, US Dept HHS, NIH, Res Triangle Pk, NC 27709 USA; Childrens Hosp, Oakland Res Inst, Oakland, CA 94609 USA; Uppsala Univ, Fac Med, SE-75105 Uppsala, Sweden; Cornell Univ, Weill Med Coll, Hosp Special Surg, New York, NY 10029 USA; Univ Penn, Ctr Expt Therapeut, Philadelphia, PA 19104 USA; Oklahoma Med Res Fdn, Oklahoma City, OK 73104 USA; Loyola Univ, Med Ctr, Maywood, IL 60153 USA; Washington Univ, Sch Med, Dept Med, St Louis, MO 63110 USA; US EPA, Res Triangle Pk, NC 27711 USA; Vanderbilt Univ, Sch Med, Dept Biochem, Nashville, TN 37240 USA; Vanderbilt Univ, Sch Med, Dept Med Pharmacol, Nashville, TN 37240 USA; OXIS Int Inc, Portland, OR 97217 USA; **Florida Inst Technol, Melbourne, FL 32901 USA**; Univ So Calif, Dept Mol Pharmacol & Toxicol, Los Angeles, CA 90089 USA; Integrated Lab Syst Inc, Res Triangle Pk, NC 27709 USA; Cornell Univ, Weill Med Coll, Dept Biochem, New York, NY 10021 USA Kadiiska@niehs.nih.gov
COUNTRY OF AUTHOR: USA; Sweden
SOURCE: FREE RADICAL BIOLOGY AND MEDICINE, (15 MAR 2005) Vol. 38, No. 6, pp. 698-710.
ISSN: 0891-5849.
PUBLISHER: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English

REFERENCE COUNT: 78
ENTRY DATE: Entered STN: 24 Mar 2005
Last Updated on STN: 24 Mar 2005
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
ED Entered STN: 24 Mar 2005
Last Updated on STN: 24 Mar 2005
AB Oxidation products of lipids, proteins, and DNA in the blood, plasma, and urine of rats were measured as part of a comprehensive, multilaboratory validation study searching for noninvasive biomarkers of oxidative stress. This article is the second report of the nationwide Biomarkers of Oxidative Stress Study using acute CCl4 poisoning as a rodent model for oxidative stress. The time-dependent (2, 7, and 16 h) and dose-dependent (120 and 1200 mg/kg ip) effects Of CCl4 on concentrations of lipid hydroperoxides, TBARS, malondialdehyde (MDA), isoprostanes, protein carbonyls, methionine sulfoxidation, tyrosine products, 8-hydroxy-2'-deoxyguano sine (8-OHdG), leukocyte DNA-MDA adducts, and DNA-strand breaks were investigated to determine whether the oxidative effects Of CCl4 would result in increased generation of these oxidation products. Plasma concentrations of MDA and isoprostanes (both measured by GG MS) and urinary concentrations of isoprostanes (measured with an **immunoassay** or LC/MS/MS) were increased in both low-dose and high-dose CCl4-treated rats at more than one time point. The other urinary markers (MDA and 8-OHdG) showed significant elevations with treatment Under three of the four conditions tested. It is concluded that measurements of MDA and isoprostanes in plasma and urine as well as 8-OHdG ill Urine are potential candidates for general biomarkers of oxidative stress. All other products were not changed by CCl4 or showed fewer significant effects. Published by Elsevier Inc.

L91 ANSWER 16 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:641984 SCISEARCH
THE GENUINE ARTICLE: 577DG
TITLE: The outer membrane localization of the Neisseria gonorrhoeae **MsrA**/B is involved in survival against reactive oxygen species
AUTHOR: Skaar E P; Tobiason D M; Quick J; Judd R C; **Weissbach H**; Etienne F; **Brot N**; Seifert H S (Reprint)
CORPORATE SOURCE: Northwestern Univ, Dept Immunol Microbiol, Feinberg Sch Med, 303 E Chicago Ave, Searle 6-458, Chicago, IL 60611 USA (Reprint); Northwestern Univ, Dept Immunol Microbiol, Feinberg Sch Med, Chicago, IL 60611 USA; Univ Montana, Div Biol Sci, Missoula, MT 59812 USA; **Florida Atlantic Univ, Ctr Mol Biol & Biotechnol, Boca Raton, FL 33431 USA**; Hosp Special Surg, New York, NY 10021 USA; Cornell Univ, Weill Med Coll, Dept Microbiol & Immunol, New York, NY 10021 USA
COUNTRY OF AUTHOR: USA
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (23 JUL 2002) Vol. 99, No. 15, pp. 10108-10113.
ISSN: 0027-8424.
PUBLISHER: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 55
ENTRY DATE: Entered STN: 16 Aug 2002
Last Updated on STN: 16 Aug 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 16 Aug 2002
Last Updated on STN: 16 Aug 2002

AB The PilB protein of Neisseria gonorrhoeae has been reported to be involved in the regulation of pilin gene transcription, but it also possesses significant homology to the peptide **methionine** sulfoxide **reductase** family of enzymes, specifically **MsrA** and **MsrB** from Escherichia coli. **MsrA** and **MsrB** in E. coli are able to reduce methionine sulfoxide residues in proteins to methionines. In addition, the gonococcal PilB protein encodes for both **MsrA** and **MsrB** activity associated with the repair of oxidative damage to proteins. In this work, we demonstrate that the PilB protein of Neisseria gonorrhoeae is not involved in pilus expression. Additionally, we show that wild-type N. gonorrhoeae produces two forms of this polypeptide, one of which contains a signal sequence and is secreted from the bacterial cytoplasm to the outer membrane; the other lacks a signal sequence and is cytoplasmic. Furthermore, we show that the secreted form of the PilB protein is involved in survival in the presence of oxidative damage.

L91 ANSWER 17 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:247691 SCISEARCH
THE GENUINE ARTICLE: 529DK
TITLE: High-quality life extension by the enzyme peptide **methionine** sulfoxide **reductase**
AUTHOR: Ruan H; Tang X D; Chen M L; Joiner M A; Sun G; **Brot N**; **Weissbach H**; Heinemann S H; Iverson L; Wu C F; Hoshi T (Reprint)
CORPORATE SOURCE: Univ Penn, Dept Physiol, 3700 Hamilton Walk, Philadelphia, PA 19104 USA (Reprint); Univ Iowa, Dept Sci Biol, Iowa City, IA 52242 USA; Univ Iowa, Dept Physiol & Biophys, Iowa City, IA 52242 USA; Cornell Univ, Hosp Special Surg, Dept Microbiol & Immunol, Weill Med Coll, New York, NY 10021 USA; **Florida Atlantic Univ, Ctr Mol Biol & Biotechnol, Boca Raton, FL 33431 USA**; Univ Jena, Fac Med, Res Unit Mol & Cellular Biophys, D-07747 Jena, Germany; Beckman Res Inst, Div Neurosci, Duarte, CA 91010 USA
COUNTRY OF AUTHOR: USA; Germany
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (5 MAR 2002) Vol. 99, No. 5, pp. 2748-2753.
ISSN: 0027-8424.
PUBLISHER: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 54
ENTRY DATE: Entered STN: 29 Mar 2002
Last Updated on STN: 29 Mar 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 29 Mar 2002
Last Updated on STN: 29 Mar 2002

AB Cumulative oxidative damages to cell constituents are considered to contribute to **aging** and **age**-related diseases. The enzyme peptide **methionine** sulfoxide **reductase** A (**MSRA**) catalyzes the repair of oxidized methionine in proteins by reducing methionine sulfoxide back to methionine. However, whether **MSRA** plays a role in the **aging** process is poorly understood. Here we report that overexpression of the **msrA** gene

predominantly in the nervous system markedly extends the lifespan of the fruit fly Drosophila. The **MSRA** transgenic animals are more resistant to paraquat-induced oxidative stress, and the onset of senescence-induced decline in the general activity level and reproductive capacity is delayed markedly. The results suggest that oxidative damage is an important determinant of lifespan, and **MSRA** may be important in increasing the lifespan in other organisms including humans.

L91 ANSWER 18 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:402394 SCISEARCH
THE GENUINE ARTICLE: 547ZP
TITLE: The mirrored **methionine** sulfoxide **reductases** of Neisseria gonorrhoeae pilB
AUTHOR: Lowther W T; **Weissbach H**; Etienne F; **Brot N**; Matthews B W (Reprint)
CORPORATE SOURCE: Univ Oregon 1229, Howard Hughes Med Inst, Inst Mol Biol, Eugene, OR 97403 USA (Reprint); Univ Oregon 1229, Dept Phys, Eugene, OR 97403 USA; **Florida Atlantic Univ, Ctr Mol Biol & Biotechnol, Boca Raton, FL 33431 USA**; Cornell Univ, Weill Med Coll, Hosp Special Surg, Dept Microbiol & Immunol, New York, NY 10021 USA
COUNTRY OF AUTHOR: USA
SOURCE: NATURE STRUCTURAL BIOLOGY, (MAY 2002) Vol. 9, No. 5, pp. 348-352.
ISSN: 1072-8368.
PUBLISHER: NATURE AMERICA INC, 345 PARK AVE SOUTH, NEW YORK, NY 10010-1707 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 50
ENTRY DATE: Entered STN: 24 May 2002
Last Updated on STN: 24 May 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
ED Entered STN: 24 May 2002
Last Updated on STN: 24 May 2002
AB **Methionine** sulfoxide **reductases** (Msr) protect against oxidative damage that can contribute to cell death. The tandem Msr domains (**MsrA** and **MsrB**) of the pilB protein from Neisseria gonorrhoeae each reduce different epimeric forms of methionine sulfoxide. The overall fold of the **MsrB** domain revealed by the 1.85 Angstrom crystal structure shows no resemblance to the previously determined **MsrA** structures from other organisms. Despite the lack of homology, the active sites show approximate mirror symmetry. In each case, conserved amino acid motifs mediate the stereo-specific recognition and reduction of the substrate. Unlike the **MsrA** domain, the **MsrB** domain activates the cysteine or selenocysteine nucleophile through a unique Cys-Arg-Asp/Glu catalytic triad. The collapse of the reaction intermediate most likely results in the formation of a sulfenic or selenenic acid moiety. Regeneration of the active site occurs through a series of thiol-disulfide exchange steps involving another active site Cys residue and thioredoxin. These observations have broad implications for modular catalysis, antibiotic drug design and continuing longevity studies in mammals.

L91 ANSWER 19 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:697551 SCISEARCH
THE GENUINE ARTICLE: 464NX
TITLE: Peptide **methionine** sulfoxide **reductase**

from Escherichia coli and Mycobacterium tuberculosis protects bacteria against oxidative damage from reactive nitrogen intermediates

AUTHOR: St John G; **Brot N**; Ruan J; Erdjument-Bromage H; Tempst P; **Weissbach H**; Nathan C (Reprint)

CORPORATE SOURCE: Stanford Univ Hosp, Dept Med, Stanford, CA 94305 USA (Reprint); Cornell Univ, Weill Med Coll, Grad Program Immunol, Dept Microbiol & Immunol, New York, NY 10021 USA; Hosp Special Surg, New York, NY 10021 USA; Sloan Kettering Inst, Prot Ctr, New York, NY 10021 USA; Sloan Kettering Inst, Program Mol Biol, New York, NY 10021 USA; **Florida Atlantic Univ, Ctr Mol Biol & Biotechnol, Boca Raton, FL 33431 USA**

COUNTRY OF AUTHOR: USA

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (14 AUG 2001) Vol. 98, No. 17, pp. 9901-9906.
ISSN: 0027-8424.

PUBLISHER: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418 USA.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 41

ENTRY DATE: Entered STN: 7 Sep 2001
Last Updated on STN: 7 Sep 2001

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 7 Sep 2001
Last Updated on STN: 7 Sep 2001

AB Inducible nitric oxide synthase (iNOS) plays an important role in host defense. Macrophages expressing MOS release the reactive nitrogen intermediates (RNI) nitrite and S-nitrosoglutathlone (GSNO), which are bactericidal in vitro at a pH characteristic of the phagosome of activated macrophages. We sought to characterize the active intrabacterial forms of these RNI and their molecular targets. Peptide **methionine** sulfoxide **reductase** (**MsrA**; EC 1.8.4.6) catalyzes the reduction of methionine sulfoxide (Met-O) in proteins to methionine (Met). E. coli lacking **MsrA** were hypersensitive to killing not only by hydrogen peroxide, but also by nitrite and GSNO. The wild-type phenotype was restored by transformation with plasmids encoding **msrA** from E. coli or M. tuberculosis, but not by an enzymatically inactive mutant **msrA**, indicating that Met oxidation was involved in the death of these cells. It seemed paradoxical that nitrite and GSNO kill bacteria by oxidizing Met residues when these RNI cannot themselves oxidize Met. However, under anaerobic conditions, neither nitrite nor GSNO was bactericidal. Nitrite and GSNO can both give rise to NO, which may react with superoxide produced by bacteria during aerobic metabolism, forming peroxynitrite, a known oxidant of Met to Met-O. Thus, the findings are consistent with the hypotheses that nitrite and GSNO kill E. coli by intracellular conversion to peroxynitrite, that intracellular Met residues in proteins constitute a critical target for peroxynitrite, and that **MsrA** can be essential for the repair of peroxynitrite-mediated intracellular damage.

L91 ANSWER 20 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:265230 SCISEARCH

THE GENUINE ARTICLE: 411WC

TITLE: Oxidative regulation of large conductance calcium-activated potassium channels

AUTHOR: Tang X D; Daggett H; Hanner M; Garcia M L; McManus O B;

Brot N; **Weissbach H**; Heinemann S H; Hoshi T (Reprint)
CORPORATE SOURCE: Univ Iowa, Dept Physiol & Biophys, BSB 5-660, Iowa City, IA 52242 USA (Reprint); Univ Iowa, Dept Physiol & Biophys, Iowa City, IA 52242 USA; Merck Res Labs, Rahway, NJ 07065 USA; Cornell Univ, Hosp Special Surg, Med Ctr, New York, NY 10021 USA; **Florida Atlantic Univ, Ctr Mol Biol & Biotechnol, Boca Raton, FL 33431 USA**; Univ Jena Klinikum, AG Mol & Zellulare Biophys, D-07447 Jena, Germany
COUNTRY OF AUTHOR: USA; Germany
SOURCE: JOURNAL OF GENERAL PHYSIOLOGY, (MAR 2001) Vol. 117, No. 3, pp. 253-273.
ISSN: 0022-1295.
PUBLISHER: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021 USA.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 126
ENTRY DATE: Entered STN: 6 Apr 2001
Last Updated on STN: 6 Apr 2001
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 6 Apr 2001
Last Updated on STN: 6 Apr 2001

AB Reactive oxygen/nitrogen species are readily generated in vivo, playing roles in many physiological and pathological conditions, such as **Alzheimer**'s disease and **Parkinson**'s disease, by oxidatively modifying various proteins. Previous studies indicate that large conductance Ca2+-activated K+ channels (BKCa or Slo) are subject to redox regulation. However, conflicting results exist whether oxidation increases or decreases the channel activity. We used chloramine-T, which preferentially oxidizes methionine, to examine the functional consequences of methionine oxidation in the cloned human Slo (hSlo) channel expressed in mammalian cells. In the virtual absence of Ca2+, the oxidant shifted the steady-state macroscopic conductance to a more negative direction and slowed deactivation. The results obtained suggest that oxidation enhances specific voltage-dependent opening transitions and slows the rate-limiting closing transition. Enhancement of the hSlo activity was partially reversed by the enzyme peptide **methionine** sulfoxide **reductase**, suggesting that the upregulation is mediated by methionine oxidation. In contrast, hydrogen peroxide and cysteine-specific reagents, DTNB, MTSEA, and PCMB, decreased the channel activity. Chloramine-T was much less effective when concurrently applied with the K+ channel blocker TEA, which is consistent with the possibility that the target methionine lies within the channel pore. Regulation of the Slo channel by methionine oxidation may represent an important link between cellular electrical excitability and metabolism.

L91 ANSWER 21 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:847602 SCISEARCH
THE GENUINE ARTICLE: 372BR
TITLE: Structure and mechanism of peptide **methionine** sulfoxide **reductase**, an "anti-oxidation" enzyme
AUTHOR: Lowther W T; **Brot N**; **Weissbach H**; Matthews B W (Reprint)
CORPORATE SOURCE: Univ Oregon, Howard Hughes Med Inst, Inst Mol Biol, Eugene, OR 97403 USA (Reprint); Univ Oregon, Dept Phys, Eugene, OR 97403 USA; Cornell Univ, Weill Med Coll, Hosp Special Surg, New York, NY 10021 USA; **Florida**

Atlantic Univ, Ctr Mol Biol & Biotechnol, Boca Raton, FL 33431 USA
COUNTRY OF AUTHOR: USA
SOURCE: BIOCHEMISTRY, (7 NOV 2000) Vol. 39, No. 44, pp. 13307-13312.
ISSN: 0006-2960.
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 41
ENTRY DATE: Entered STN: 2000
Last Updated on STN: 2000
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
ED Entered STN: 2000
Last Updated on STN: 2000
AB Peptide **methionine** sulfoxide **reductase** (**MsrA**) reverses oxidative damage to both free methionine and methionine within proteins. As such, it helps protect the host organism against stochastic damage that can contribute to cell death. The structure of bovine **MsrA** has been determined in two different modifications, both of which provide different insights into the biology of the protein. There are three cysteine residues located in the vicinity of the active site. Conformational changes in a glycine-rich C-terminal tail appear to allow all three thiols to come together and to participate in catalysis. The structures support a unique, thiol-disulfide exchange mechanism that relies upon an essential cysteine as a nucleophile and additional conserved residues that interact with the oxygen atom of the sulfoxide moiety.

L91 ANSWER 22 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:458529 SCISEARCH
THE GENUINE ARTICLE: 322UA
TITLE: Thiol-disulfide exchange is involved in the catalytic mechanism of peptide **methionine** sulfoxide **reductase**
AUTHOR: Lowther W T; **Brot N; Weissbach H;** Honek J F; Matthews B W (Reprint)
CORPORATE SOURCE: Howard Hughes Med Inst, Inst Mol Biol, Eugene, OR 97403 USA (Reprint); Univ Oregon, Dept Phys, Eugene, OR 97403 USA; Cornell Univ, Med Ctr, Hosp Special Surg, New York, NY 10021 USA; **Florida Atlantic Univ, Ctr Mol Biol & Biotechnol, Boca Raton, FL 33431 USA**; Univ Waterloo, Dept Chem, Waterloo, ON N2L 3G1, Canada
COUNTRY OF AUTHOR: USA; Canada
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (6 JUN 2000) Vol. 97, No. 12, pp. 6463-6468.
ISSN: 0027-8424.
PUBLISHER: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 53
ENTRY DATE: Entered STN: 2000
Last Updated on STN: 2000
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
ED Entered STN: 2000
Last Updated on STN: 2000

AB Peptide **methionine** sulfoxide **reductase** (**MsrA**; EC 1.8.4.6) reverses the inactivation of many proteins due to the oxidation of critical methionine residues by reducing methionine sulfoxide. Met(O), to methionine. **MsrA** activity is independent of bound metal and cofactors but does require reducing equivalents from either DTT or a thioredoxin-regenerating system. In an effort to understand these observations. the four cysteine residues of bovine **MsrA** were mutated to serine in a series of permutations. An analysis of the enzymatic activity of the variants and their free sulfhydryl states by mass spectrometry revealed that thiol-disuifide exchange occurs during catalysis. In particular, the strictly conserved Cys-72 was found to be essential for activity and could form disulfide bonds, only upon incubation with substrate, with either Cys-218 or Cys-227, located at the C terminus. The significantly decreased activity of the Cys-218 and Cys-227 variants in the presence of thioredoxin suggested that these residues shuttle reducing equivalents from thioredoxin to the active site. A reaction mechanism based on the known reactivities of thiols with sulfoxides and the available data for **MsrA** was formulated. In this scheme. Cys-72 acts as a nucleophile and attacks the sulfur atom of the sulfoxide moiety, leading to the formation of a covalent, tetracoordinate intermediate. Collapse of the intermediate is facilitated by proton transfer and the concomitant attack of Cys-218 on Cys-72, leading to the formation of a disulfide bond. The active site is returned to the reduced state for another round of catalysis by a series of thiol-disulfide exchange reactions via Cys-227, DTT, or thioredoxin.

L91 ANSWER 23 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:553989 SCISEARCH
THE GENUINE ARTICLE: 313NH
TITLE: Thiol-disulfide exchange is involved in the catalytic mechanism of peptide **methionine** sulfoxide **reductase.**
AUTHOR: Lowther W T (Reprint); **Brot N**; Gay L S; Wang M; **Weissbach H**; Mathews B W
CORPORATE SOURCE: Univ Oregon, Dept Phys, HHMI, Inst Mol Biol, Eugene, OR 97403 USA; Cornell Univ, Med Ctr, Hosp Special Surg, New York, NY 10021 USA; **Florida Atlantic Univ, Ctr Mol Biol & Biotech, Boca Raton, FL 33431 USA**
COUNTRY OF AUTHOR: USA
SOURCE: FASEB JOURNAL, (11 MAY 2000) Vol. 14, No. 8, pp. A1420-A1420. MA 623.
ISSN: 0892-6638.
PUBLISHER: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0
ENTRY DATE: Entered STN: 2000
Last Updated on STN: 2000
ED Entered STN: 2000
Last Updated on STN: 2000

L91 ANSWER 24 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:234538 SCISEARCH
THE GENUINE ARTICLE: 409UQ
TITLE: Peptide **methionine** sulfoxide **reductase** : Biochemistry and physiological role

AUTHOR: **Brot N (Reprint); Weissbach H**
CORPORATE SOURCE: Cornell Univ, Hosp Special Surg, Weill Med Coll, New York, NY 10021 USA (Reprint); **Florida Atlantic Univ, Ctr Mol Biol & Biotechnol, Boca Raton, FL 33431 USA**
COUNTRY OF AUTHOR: USA
SOURCE: BIOPOLYMERS, (2000) Vol. 55, No. 4, pp. 288-296. ISSN: 0006-3525.
PUBLISHER: JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 61
ENTRY DATE: Entered STN: 30 Mar 2001
Last Updated on STN: 30 Mar 2001
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 30 Mar 2001
Last Updated on STN: 30 Mar 2001

AB The oxidation of methionine to methionine sulfoxide both in vivo and in vitro can lead to the loss of biological activity in a variety of proteins. This loss of activity can be reversed by an enzyme called **methionine** sulfoxide **reductase.** The gene for this enzyme has been cloned and sequenced from a variety of prokaryotic and eukaryotic cells, and the deduced amino acid sequence is very highly conserved. The mechanism of action of the bovine enzyme has been shown to involve a critical cysteine residue located at position 72 of the protein. In addition to its role as a "repair" enzyme, other evidence suggests that the enzyme may be involved in bacterial adherence and regulation of protein activity. (C) 2001 John Wiley & Sons, Inc.

L91 ANSWER 25 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:58865 SCISEARCH
THE GENUINE ARTICLE: 156LL
TITLE: Regulation of voltage-dependent K+ channels by methionine oxidation: effect of nitric oxide and vitamin C
AUTHOR: Ciorba M A; Heinemann S H; **Weissbach H; Brot N**; Hoshi T (Reprint)
CORPORATE SOURCE: Univ Iowa, Dept Physiol & Biophys, Iowa City, IA 52242 USA (Reprint); Max Planck Gesell, Res Unit Mol & Cellular Biophys, D-07747 Jena, Germany; **Florida Atlantic Univ, Dept Biol Sci, Boca Raton, FL 33431 USA**; Cornell Univ, Hosp Special Surg, Med Ctr, New York, NY 10021 USA
COUNTRY OF AUTHOR: USA; Germany
SOURCE: FEBS LETTERS, (8 JAN 1999) Vol. 442, No. 1, pp. 48-52. ISSN: 0014-5793.
PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 37
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 1999
Last Updated on STN: 1999

AB Methionine oxidation is known to alter functional properties of a transient A-type potassium channel expressed in Xenopus oocytes. We show here that nitric oxide (NO) slows down the K+ channel inactivation time course by oxidizing a critical methionine residue in the inactivation hall

domain of the channel protein. We also demonstrate that the channel protein is protected from methionine oxidation by the enzyme **methionine** sulfoxide **reductase** and the antioxidant vitamin C, (C) 1999 Federation of European Biochemical Societies.

L91 ANSWER 26 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:613477 SCISEARCH
THE GENUINE ARTICLE: 224QQ
TITLE: Molecular cloning and functional expression of a human peptide **methionine** sulfoxide **reductase** (hMsrA)
AUTHOR: Kuschel L; Hansel A; Schoherr R; **Weissbach H**; **Brot N**; Hoshi T; Heinemann S H (Reprint)
CORPORATE SOURCE: Klinikum Friedrich Schiller Univ Jena, Arbeitsgrp Mol & Zellulare Biophys, Drackendorfer Str 1, D-07747 Jena, Germany (Reprint); Klinikum Friedrich Schiller Univ Jena, Arbeitsgrp Mol & Zellulare Biophys, D-07747 Jena, Germany; **Florida Atlantic Univ, Dept Biol Sci, Boca Raton, FL 33431 USA**; Cornell Univ, Med Ctr, Hosp Special Surg, New York, NY 10021 USA; Univ Iowa, Dept Physiol & Biophys, Iowa City, IA 52242 USA
COUNTRY OF AUTHOR: Germany; USA
SOURCE: FEBS LETTERS, (30 JUL 1999) Vol. 456, No. 1, pp. 17-21. ISSN: 0014-5793.
PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 17
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
ED Entered STN: 1999
Last Updated on STN: 1999
AB Oxidation of methionine residues in proteins to methionine sulfoxide can be reversed by the enzyme peptide **methionine** sulfoxide **reductase** (**MsrA**, EC 1.8.4.6). We cloned the gene encoding a human homologue (hMsrA) of the enzyme, which has an 88% amino acid sequence identity to the bovine version (bMsrA), With dot blot analyses based on RNA from human tissues, expression of hMsrA was found in all tissues tested, with highest mRNA levels in adult kidney and cerebellum, followed by liver, heart ventricles, bone marrow and hippocampus. In fetal tissue, expression was highest in the liver. No expression of hmsr A was detected in leukemia and lymphoma cell lines. To test if hMsrA is functional in cells, we assayed its effect on the inactivation time course of the A-type potassium channel ShC/B since this channel property strongly depends on the oxidative state of a methionine residue in the N-terminal part of the polypeptide, Go-expression of ShC/B and hMsrA in Xenopus oocytes significantly accelerated inactivation, showing that the cloned enzyme is functional in an in vivo assay system. Furthermore, the activity of a purified glutathione-S-transferase-hMsrA fusion protein was demonstrated in vitro by measuring the reduction of [H-3]N-acetyl methionine sulfoxide, (C) 1999 Federation of European Biochemical Societies.

L91 ANSWER 27 OF 28 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1997:663373 SCISEARCH
THE GENUINE ARTICLE: XU455

TITLE: Modulation of potassium channel function by methionine oxidation and reduction
AUTHOR: Ciorba M A (Reprint); Heinemann S H; **Weissbach H**; **Brot N**; Hoshi T
CORPORATE SOURCE: UNIV IOWA, DEPT PHYSIOL & BIOPHYS, IOWA CITY, IA 52242; MAX PLANCK GESELL, RES UNIT MOL & CELLULAR BIOPHYS, D-07747 JENA, GERMANY; **FLORIDA ATLANTIC UNIV, DEPT BIOL SCI, BOCA RATON, FL 33431**; CORNELL UNIV, HOSP SPECIAL SURG, MED CTR, NEW YORK, NY 10021
COUNTRY OF AUTHOR: USA; GERMANY
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2 SEP 1997) Vol. 94, No. 18, pp. 9932-9937.
ISSN: 0027-8424.
PUBLISHER: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 40
ENTRY DATE: Entered STN: 1997
Last Updated on STN: 1997
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 1997
Last Updated on STN: 1997

AB Oxidation of amino acid residues in proteins can be caused by a variety of oxidizing agents normally produced by cells. The oxidation of methionine in proteins to methionine sulfoxide is implicated in **aging** as well as in pathological conditions, and it is a reversible reaction mediated by a ubiquitous enzyme, peptide **methionine** sulfoxide **reductase**. The reversibility of methionine oxidation suggests that it could act as a cellular regulatory mechanism although no such in vivo activity has been demonstrated. We show here that oxidation of a methionine residue in a voltage-dependent potassium channel modulates its inactivation. When this methionine residue is oxidized to methionine sulfoxide, the inactivation is disrupted, and it is reversed by coexpression with peptide **methionine** sulfoxide **reductase**. The results suggest that oxidation and reduction of methionine could play a dynamic role in the cellular signal transduction process in a variety of systems.

L91 ANSWER 28 OF 28 CONFSCI COPYRIGHT 2006 CSA on STN
ACCESSION NUMBER: 84:18966 CONFSCI
DOCUMENT NUMBER: 84030366
TITLE: Reactivation by E. coli **methionine** sulfoxide peptide **reductase** of alpha-1-antitrypsin inactivated by cigarette smoke and hydrogen peroxide
AUTHOR: James, H.L.; **Brot, N.**; Janoff, A.; Carp, H.; Fliss, H.; **Weissbach, H.**
CORPORATE SOURCE: Univ. Texas Health Cent., Tyler, TX, USA
SOURCE: Abstracts in: "American Review of Respiratory Disease", Apr. 1984, American Lung Association, 1740 Broadway, New York, NY 10019, USA, ISSN 0003-0805.
Meeting Info.: 842 0019: American Lung Association, American Thoracic Society and Congress of Lung Association Staff Annual Meeting (8420019). Miami Beach, **FL** (USA). 20-23 May 84. American Thoracic Society (ATS); American Lung Association (ALA); Congress of Lung Association Staff (CLAS).
DOCUMENT TYPE: Conference

FILE SEGMENT: DCCP
LANGUAGE: UNAVAILABLE

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